

Health, Risk Factors and Death in Middle-Aged Males

with particular reference to
effects and consequences of alcohol

BO PETERSSON

—



Malmö 1983

—

Lund

—

HEALTH, RISK FACTORS AND DEATH IN MIDDLE-AGED MALES
with particular reference to effects and consequences of alcohol

AKADEMISK AVHANDLING

som med vederbörligt tillstånd av Medicinska Fakulteten vid Lunds
Universitet för avläggande av medicine doktorsexamen kommer att
offentligen försvaras i universitetsklinikernas aula, Allmänna
Sjukhuset, Malmö, fredagen den 9 december, 1983, kl 9.00.

av

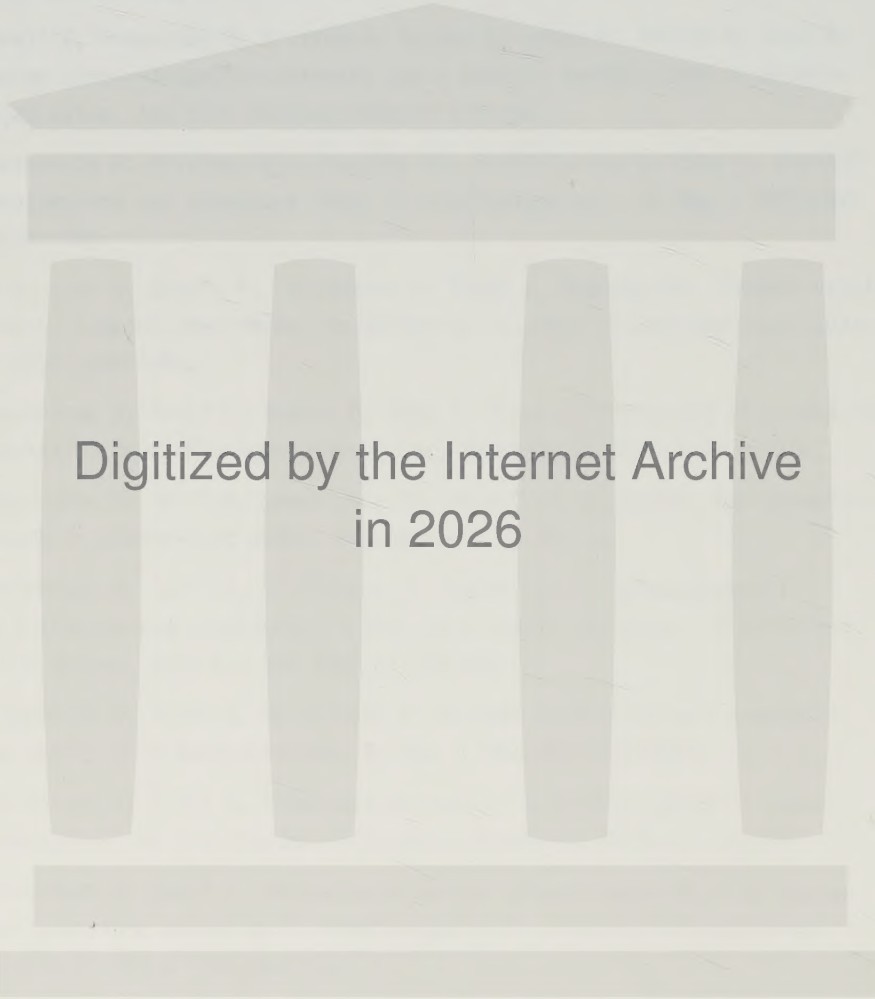
Bo Petersson
med lic, Sm

This thesis is based on the following papers:

- I. Petersson B, Trell E, Kristenson H, Fex G, Yettra M, Hood B. Comparison of gamma-glutamyltransferase and other health screening tests in average middle-aged males, heavy drinkers and alcohol non-users. Scand J Clin Lab Invest 1983;43:141-149.
- II. Trell E, Petersson B, Kristenson H, Fex G, Larne P, Yettra M, Hood B. Serum gamma-glutamyltransferase and a somatic health score in middle-aged males. Ann Clin Biochem 1980;17:134-139.
- III. Petersson B, Kristenson H, Sternby NH, Trell E, Fex G, Hood B. Alcohol consumption and premature death in middle-aged men. Br Med J 1980;280:1403-1406.
- IV. Petersson B, Krantz P, Kristenson H, Trell E, Sternby NH. Alcohol-related death: a major contributor to mortality in urban middle-aged men. Lancet 1982;2:1088-1090.
- V. Petersson B, Trell E, Krantz P, Hood B. Major determinants of premature mortality in middle-aged urban males. Accepted in Am J Publ Health.
- VI. Petersson B, Trell E, Henningsen NC, Hood B. Risk factors for premature death in middle-aged males. Submitted to Br Med J.
- VII. Petersson B, Trell E, Kristenson H. Comparison of gamma-glutamyltransferase and questionnaire test as alcohol indicators in different risk groups. Drug Alc Dep 1983;11:279-286.
- VIII. Petersson B, Trell E, Kristenson H. Alcohol abstention and premature mortality in middle-aged men. Br Med J 1982;285:1457-1459.
- IX. Petersson B, Trell E. Premature mortality in middle-aged men: serum cholesterol as risk factor. Klinische Wochenschr 1983;63:795-801.
- X. Petersson B, Trell E. Raised serum urate concentration as risk factor for premature mortality in middle-aged men: relation to death from cancer. Br Med J 1983;287:7-9.



To
Gunnel, Sofia and Filip



Digitized by the Internet Archive
in 2026

https://archive.org/details/IA41546727_0060

<u>CONTENTS</u>	Page
INTRODUCTION	7
MORTALITY AS MEASURE OF ILL-HEALTH	8
AIMS OF THE STUDY	9
MATERIAL AND METHODS	10
1. Department of Preventive Medicine in Malmö	10
2. Population	11
3. Screening investigation	11
Physiological measurements	11
Biochemical analyses	12
Questionnaire	12
4. Intervention programs	13
5. Mortality follow-up	13
6. Indicators of alcohol abuse	14
7. Statistical methods	15
RESULTS	
ENTRY CHARACTERISTICS OF SERUM-GGT, OTHER SCREENING ANALYTES AND SUBGROUPS OF ALCOHOL CONSUMPTION (PAPERS I AND II)	17
Discussion	19
CHARACTERIZATION OF THE MORTALITY (PAPERS III, IV AND V)	20
1. Total mortality	20
2. Alcohol-related death	20
3. Coronary heart disease death	23
4. Suicides	23
5. Cancer death	25
6. Intervention measures among the deceased subjects	27
7. Discussion	28
ENTRY CHARACTERISTICS IN RELATION TO MORTALITY	31
1. Non-participation (Paper V)	31
Discussion	31
2. Mortality in males with an alcohol-positive history (Paper IV)	31
Discussion	32

	Page
3. Entry characteristics and total mortality (Paper VI)	32
Discussion	33
4. Entry characteristics and alcohol-related death (Papers III, VI and VII)	33
Discussion	34
5. Alcohol abstention and mortality (Paper VIII)	36
Discussion	37
6. Entry characteristics in relation to death in coronary heart disease (Papers VI and IX)	37
Discussion	38
7. Entry characteristics and cancer death (Papers VI, IX and X)	39
Discussion	40
CONCLUDING REMARKS	43
ACKNOWLEDGEMENTS	48
REFERENCES	49
PAPERS I -X	57

INTRODUCTION

There is now a general agreement, not only among dedicated advocates of preventive medicine, that "many common diseases are capable of being prevented by means that have not yet been fully implemented" (Doll 1983). This in particular applies to the new, non-infectious epidemics which have spread, so far most dramatically among middle-age men, through Western societies during the last century and which are all essentially avoidable on an individual level by "practical steps that ... mostly require changes in personal behaviour and the factors that influence it" (Doll 1983), e.g. cardiovascular disorders, adult diabetes mellitus, overweight, alcohol and tobacco smoking complications, and cancer.

In some of these conditions, most notably coronary heart disease, the preventive approach would even seem to be the only way in which efficient improvement can be brought about. The important role of coronary heart disease for mortality in males is also the reason why previous epidemiological studies have been predominantly concerned with this subject, e.g. the Seven Countries study (Keys 1980) and the Framingham study (Dawber 1980). In Sweden, Tibblin's investigation of men born 1913 from Gothenburg (1967) has been pioneering and likewise mainly focussed upon the cardiovascular disease field.

When the Malmö Preventive Programme was started in 1974-1975, its aim was to correspond to the aforementioned more complex and multifaceted spectrum of ill-health in the urban middle-aged male population to which it was primarily directed (Trell 1983), where coronary heart disease is not the only prominent attributor to morbidity but there is also a prominent morbidity in cancer and in complications of alcohol. An increase in alcohol consumption and in alcohol-related disabilities (Edwards et al. 1977) had been evident during the preceding twenty years, why attempts at tracing high consumers with the aim of intervention were included. The resulting programme for indication and prevention of alcohol-related disabilities has been reported by Kristenson (1982).

MORTALITY AS MEASURE OF ILL-HEALTH

It has been argued that mortality is of little value as measure of ill-health in younger ages, because of the low rate of death that can be regarded as premature, i.e. occurring too early in life (Bolander 1980). However, the study of death as an end-point has many advantages, as it is easy to measure and more complete in this respect compared with morbidity. As stated by Doll (1983), death "is unequivocal and the medical and social changes to reduce it nearly always reduce the corresponding morbidity as well". This statement points to connections between mortality and morbidity, which may not exist for chronic diseases with a low death rate, such as rheumatoid arthritis, but may well exist for cardiovascular diseases, cancer and alcohol-related conditions, all of which are disorders with a considerable fatality rate. Changes in death rates may also be sensitive indicators of important factors in the environment. Furthermore, it has been stated that mortality statistics are currently the only basis for systematic comprehensive comparison between countries as well as for analysis of long-term secular trends (Fox et al. 1983).

One of the most important epidemiological approaches to disease control is identification of risk factors and determinants so that rational preventive measures can be instituted and evaluated (Fox et al. 1983). Mortality reflects the most pronounced stages of diseases, plausibly with more pronounced risk factor patterns.

Regional and national mortality rates may also be utilized for allocation of health care resources; which is discussed in a recent report from the Swedish Institute for Rationalisation and Planning of the Health Services (SPRI 1983). The limitations of this method have been pointed out by Goldacre and Harris 1980. Moreover, the official death statistics have many inherent deficiencies, as shown by Bolander (1981), in particular a well known under-reporting of alcohol-related death. All this emphasizes the need for further analyses of the structure and pattern of various parts of the all-cause mortality and its respective risk factors and determinants in well defined, age- and sex-uniform, total population samples.

AIMS OF THE STUDY

The aims of the present investigation were to analyse risk factors and mortality 0-7 years after invitation to a screening investigation, in an unselected population of urban middle-age males, in relation to the screening characteristics and with emphasis on the role of alcohol in comparison with cardiovascular and neoplastic diseases; in particular

- the influence of alcohol on the screening variables
- the role of alcohol as causative factor for mortality and comparison of this estimate with official statistics
- characterization of the non-participants in comparison with the participants
- comparison of biochemical estimates and questionnaire method as alcohol indicators
- comparison of alcohol indicators as risk factors with other "classical" risk factors in relation to premature death
- evaluation of alcohol abstention in relation to premature death
- assessment of risk factors for death due to cancer and coronary heart disease

MATERIAL AND METHODS

1. DEPARTMENT OF PREVENTIVE MEDICINE IN MALMÖ

The Malmö General Hospital is a university hospital and the only general hospital in the city, which has a population of about 230,000.

Since 1975, a Department of Preventive Medicine has been in operation, organized as a section within the Department of Internal Medicine. A detailed description of the planning and design of the Preventive Medical Unit and its functions has been given elsewhere (Trell 1983).

Fig 1 summarizes the composition and volumes of the screening and out-patient clinic services of the department. 10,000 mammographies and 5,000 new medical screening investigations are performed per year.

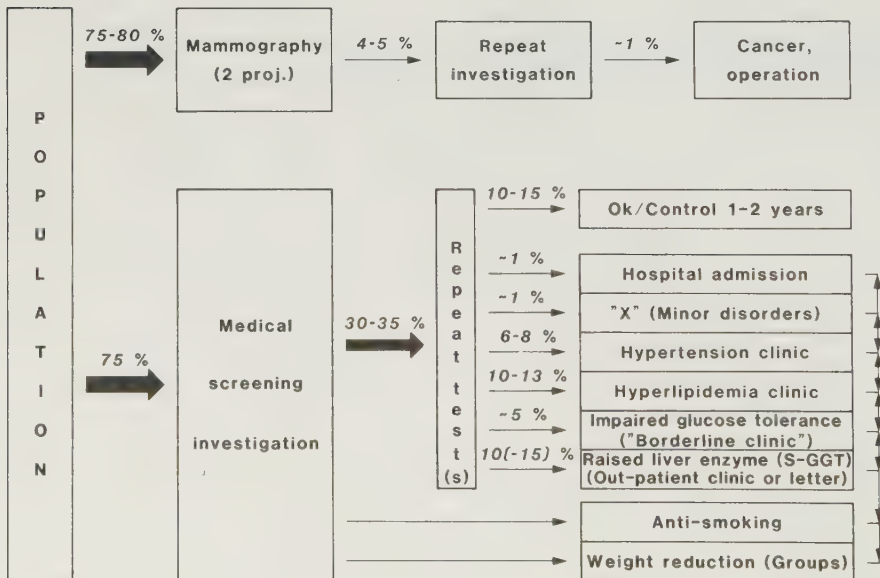


Fig 1: Flow-chart of Department of Preventive Medicine in Malmö.

2. POPULATION

The papers in this thesis include different parts of the male birth-year cohorts 1926-1932. All male Malmö residents belonging to these cohorts were invited to the screening by letter, twice if necessary, and examined consecutively from the end of 1974 until mid -79. The names and addresses of the males in the cohorts were provided by the population census office of the city of Malmö.

The age at screening, or appointment to screening in case of the non-participants, was, with few exceptions, 46-48 years.

In total, the seven birth-year cohorts 1926-1932 comprised 19,353 males, which were all invited. The ultimate number of participants is - at present - 7,948; i.e. a participation rate of 76.8%. In some of the earlier papers, a slightly lower participant number has been given, corresponding to all those who were retrieved from the computer at that time. However, some participants have subsequently attended the screening and their data then been transferred to the computer files. These minor discrepancies do not affect the performed calculations or obviate any conclusions drawn.

3. SCREENING INVESTIGATION

All examinations were performed by nurses, in the morning after an overnight fast. Venous blood samples were drawn in the supine position.

Physiological measurements

Height and weight were measured, and a relative weight index ($A/I\text{-weight} = \text{Actual} / \text{Ideal weight}$) was calculated. The ideal weight references were obtained from tables by Lindberg et al. (1956). The triceps skinfold, the pulse at 0 minutes, and systolic and diastolic blood pressure at 0 minutes and 10 minutes, standing and recumbent, were recorded. All blood pressures were measured by a mercury manometer to the nearest 5 mm Hg. The systolic pressure was recorded when the sounds appeared and the diastolic pressure at phase five of the Korotkoff sound. A twelve-lead electrocardiogram was obtained as well as simple pulmonary function tests.

Biochemical analyses

All biochemical analyses were performed according to standard methods by the Department of Clinical Biochemistry.

Serum gamma glutamyltransferase (GGT) was determined according to the recommendations of the Scandinavian Enzyme Committee (1976). Serum concentrations of sodium, potassium and calcium were determined by flame photometry, triglyceride, cholesterol, urate and glucose were determined enzymatically, albumin was measured with a dye-binding method (bromocresol-green) and creatinine with Jaffe's alkaline picrate method (Paper I). Plasma insulin was measured as immuno-reactive insulin by a standard radio-immuno assay.

Alcohol concentration (blood, urine or tissue) in connection with forensic autopsy was determined by gas chromatography.

Questionnaire

Each participant answered a questionnaire consisting of about 260 questions, with yes-no-don't know alternatives (the two latter registered as "no"), and distributed by a card-box or on-line computer system (Trell et al. 1982). These questions include family and medical history, psycho-social conditions, physical activity, smoking habits (Janzon et al. 1981), and others.

In the present study, the smoking habits were categorized in four groups: former smoker or never-smoker (R 0), 1-10 cigarettes/day (R 1), 11-20 cigarettes/day (R 2) and ≥ 21 cigarettes/day (R 3). Pipe, cigar and mixed smokers were referred to these groups according to the relation; 1 cigarette = 1 gram of tobacco. For classification of the smoking habits, the questionnaire data were supplemented by notations made by the nurses at screening, in order to obtain as correct grouping as possible.

Included in the questionnaire was also the question: "Are you a teetotaler?", and nine questions for attitudes to alcohol, a variant to the brief MAST (Michigan Alcoholism Screening Test); the Mm-MAST (Malmö modification of the brief MAST) (Kristenson and Trell 1982). These questions are shown in paper VII, table I. For each individual, the affirmative answers were added to a score, which consequently ranged from 0-9.

4. INTERVENTION PROGRAMS

As summarized in fig 1, planned intervention programs were linked with the screening investigation. All values exceeding the applied cut-off limits were intervened on only if verified in a repeat test. Furthermore, due to considerable intercorrelations between many of the screening variables more than one may exceed the cut-off limit in two consecutive determinations, and were therefore ranked in terms of importance/therapy facilities in the following order: 1) hypertension 2) GGT elevation 3) impaired glucose tolerance 4) hyperlipidemia. Overt disease states, such as manifest diabetes mellitus, were referred to the respective hospital departments. Furthermore, group-mediated programmes for anti-smoking, overweight counselling, and a small clinic for miscellaneous conditions (fig 1) have been instituted.

Subjects with two consecutive elevated GGT levels were allocated randomly to intervention and control groups of about equal size (Kristenson 1982).

5. MORTALITY FOLLOW-UP

Information on deaths after screening, or appointment to screening in case of the non-participants, was obtained from a register at the Department of Pathology at the General Hospital, which covers all deaths in Malmö residents.

The follow-up time varies in the different papers. The longest follow-up for the total cohort of participants and non-participants was until the end of 1981, i.e. a maximum of seven years (Paper V) and for participants alone until the end of 1982, i.e. a maximum of eight years (Paper VI).

The autopsy rate was high (87.7%, Paper V). Autopsies were performed by the Department of Pathology and the Department of Forensic Medicine. A forensic autopsy is, in Sweden, performed on the request of the police, in case of violent death or otherwise when the cause of death is difficult to establish e.g., in most cases, death outside hospital.

The ages at death in the participant group in paper VI (n=218) were 46-56, mean 51 years.

In order to estimate the magnitude of the loss from follow-up, a nationwide computerized matching of the original invitation files to actual files was made by mid -81, by using the Swedish ten-digit personal identification number (birth date plus four digits). In this way, only a few additional deaths were retrieved, and the number lost to follow-up was small. Sixty-five subjects out of the original 10,353 invited (0.6%) were lost for follow-up, and of these, 47 had emigrated (Paper V). This loss is ignored in the calculations, but the additional deaths are included in the analyses in papers V och VI. The time between mid -81 and end of 1982 is thus not covered for the deaths or losses from follow-up occurring outside Malmö.

All available information pertaining to the deceased subjects and their causes of death was recollected. Special interest was devoted to information on alcohol background. Examples of the utilized sources are: screening protocols for participants; hospital records, including those of the Department of Alcohol Diseases; police protocols (in the forensic autopsy group); death certificates; and official death codes from the Swedish National Central Bureau of Statistics (SCB) according to the ICD classification (ICD 1967).

A (revised) cause of death was established and arranged in one of the following categories:

- 1) cancer, 2) coronary heart disease, 3) other cardiovascular diseases,
- 4) alcohol-related, 5) miscellaneous, 6) unknown.

The delineations of these groups are discussed below. Lack of data may have influenced the accuracy of this classification in some subjects, and a few subjects might have changed category from an early to a later stage of the study due to additional supply of data.

6. INDICATORS OF ALCOHOL ABUSE

The term "alcohol abuse" and "alcohol abuser" are rejected by Keller in his "Tentative lexicon for alcohol-related disabilities" (1977) as a Scandinavism. However, these are the designations most commonly encountered in police protocols, hospital records, etc, alongside with "alcoholism", "alcoholic" and "chronic alcoholic"; terms likewise disclaimed by Keller. It is thus admitted that these terms lack exact definitions.

All dead subjects and their living controls were checked as to their possible contacts with the Department of Alcohol Diseases (DAD) at the Malmö General Hospital. If they - at any one time - had been in contact with this department, they were classified as "registered" at the Alcohol Department (RAD).

A subject, who was either RAD or in any source characterized as an alcohol abuser or alcoholic was in the present context labelled as having an "alcohol-positive history" (APH), or, for short, "alcoholic". No exact quantification of amounts of alcohol consumed per day or symptoms of the alcohol dependency syndrome are thus implemented in this term.

Also, some subjects with elevated GGT value at screening, which at subsequent evaluation was considered to be due to alcohol, were included in the APH group.

7. STATISTICAL METHODS

Comparisons of mean values were performed by Student's t-test (Paper I), and of proportions by chi-square test with one degree of freedom (Papers I and V).

Risk factors were analysed by comparing the dead subjects either with a control group, matched 2:1 for age and screening data and/or the whole population of screening attenders belonging to the same birth-year cohorts.

In papers IX and X the risk factor analyses were performed by test for trend in contingency tables (Armitage 1971), using quintile groups of the tested variables for the whole background population as reference and comparing the exact numbers of subjects and controls in the respective quintiles in the statistical calculations. The same method of test for trend in contingency tables was also used in paper VIII.

The risk factor analyses in paper VI were performed by Fisher's permutation test (Bradley 1968). The comparisons with respect to one risk factor (main or foreground variable) when a second one (background variable) was eliminated, were performed by Mantel's test (1963). However, instead of chi-square approximation, a more accurate method was used, based on the Edgeworth expansion (Cramér 1946). The probabilities for the respective death categories were estimated as functions of single risk factors under order restriction (Barlow et al. 1972),

and as functions of several factors by use of a logistic model. Estimation under order restriction was also applied on the probabilities obtained by logistic model, by considering the logistic model probability as a new variable (Paper VI).

Sensitivity, specificity, positive predictive value, negative predictive value and efficiency for GGT and Mm-MAST were calculated in paper VII according to Galen and Gambino (1975).

RESULTS

ENTRY CHARACTERISTICS OF SERUM-GGT, OTHER SCREENING ANALYTES AND SUBGROUPS OF ALCOHOL CONSUMPTION (PAPERS I AND II).

Papers I and II compare the entry characteristics of the study population in a representative subsample consisting of the birth-year cohorts 1926-1929 (4.732 participants), with particular emphasis on the variations of the screening analytes in subgroups with different levels of GGT and/or characterized alcohol consumption.

These study groups are defined in the respective papers, and comprise the following categories:

1) IOGT-teetotallers (n=51), 2) self-asserted alcohol abstainers (n=100), 3) GGT below median (n=2.196), 4) average screening attenders (n=4.763), 5) members in group 4 with screening (GGT) in top decedtile (n=171), 6) members in group 5 classified as alcohol-related (A, n=136), and 7) an extra group consisting of 574 consecutive randomly selected males born in 1930 (half of the participants of this birth-year cohort) in which a quintile score was tested (Paper II).

In paper I, mean values, standard deviations and frequencies of borderline high values were compared. There were highly significant differences between the whole study population and the IOGT members for recumbent systolic blood pressure after 10 min rest, hematocrit serum albumine, serum creatinine, cholesterol and GGT. Between the group of increased GGT on the one hand and the teetotallers and, to a lesser extent, the average men on the other hand, the differences of all these tests except albumin tended to be still more significant, and in addition there were significant differences in A/I weight, pulse, recumbent diastolic blood pressure after 10 min rest, serum urate, fasting blood glucose, and serum triglycerides. In the cases of GGT in the top decedtile with confirmed alcohol background the differensens were even higher than in the whole group of increased GGT. The tests which did not show equally significant differences between the groups include triceps skinfold thickness, pulse after 10 min rest, serum sodium, potassium and calcium.

In general, the self-reported abstainers and the group of GGT below the median had very similar values as the IOGT members.

Statistically highly significant differences were also found in a frequency comparison of borderline high test levels in the A subgroup of screening GGT in the top decentile, the whole screening population, and the IOGT teetotallers, e.g. of the systolic and diastolic blood pressure at 10 min, relative body weight, resting pulse, serum urate, blood glucose at 120 min in oral glucose tolerance test and serum triglycerides. The rate of elevated values was higher in the former group than in the whole cohort, and lowest in the teetotallers. These results show that even small numerical differences of mean values were associated with a more pronounced redistribution of the test levels.

In paper II, such redistributions were compared in a different way, i.e. by quintile comparison. To that end, the distributions of the tests in the whole study population were divided in quintiles, and the values of the same variables in two of the other study groups, viz group 3 and group 5, were allocated to these quintiles. Pronounced divergences were found in the distributions of pulse after 10 min rest, recumbent systolic blood pressure at 10 min, recumbent diastolic blood pressure at 10 min, relative body weight, blood glucose and serum insuline 120 min in oral glucose tolerance test, serum triglycerides, urate, asparagine aminotransferase (ASAT) and alanine-aminotransferase (ALAT); with a smaller percentage of the high GGT group in the lower reference quintiles and larger percentage in the higher quintiles (and vice versa in the low GGT group).

The differences in test value distributions between the study groups were more accurately demonstrated by this quintile comparison method than by the mean values or the frequencies of abnormal levels. Furthermore, results which in this way have been mathematically normalized can be directly added to a combined score. This was tested for the aforementioned ten variables in each of the members of a random half of the 1930 birth-year cohort. The sum scores showed an approximately normal distribution in this group and a good linear correlation with the GGT values in the same males; particularly in the lower end of the ranges of both these screening determinations.

DISCUSSION

The here examined variables as well as the utilized statistical evaluation and graphical representation techniques are commonly applied in the assessment and comparison of risk factors. Besides these methodological motivations, the description of their patterns in the premorbid screening population at the time of entrance in the study may be of interest per se, since, as discussed in the respective papers, the findings parallel previous reports on the associations between alcohol and certain commonly measured biometrical variables; both positive (e.g. with blood pressure, hematocrit, serum urate, cholesterol and triglycerides, fasting blood glucose and blood glucose in oral glucose tolerance tests, pulse rate and body weight) and inverse, e.g. with serum creatinine.

The same co-variations were also seen for GGT without certified alcohol background, why it is not clear how much of the variability that may be ascribed to alcohol and how much to other potentially GGT-increasing agents, such as drugs or calories. Nevertheless, both GGT and the other biometrical screening variables and the various characterized alcohol consumption subgroups in the screening population were important entry characteristics in the present prospective investigation of risk factors for the premature mortality end-point. Their interrelations at the initial stages of the study as well as the various methods of evaluating and representing them that were used throughout the study period are therefore important to define and describe.

CHARACTERIZATION OF THE MORTALITY (PAPERS III, IV AND V)

In this section, the analysis of death causes is described. These findings are partly updated so that they apply to the participants with the longest follow-up, i.e. the group analysed in paper VI. However, paper III is included as a case file in order to demonstrate the actual structure and modes of death in a total consecutive sample of the earliest premature mortality that occurred in the study population.

1. Total mortality

The mortality analysis for participants and non-participants, followed until the end of 1981 (Paper V, table I), showed that alcohol-related deaths constituted the leading cause of death, followed by cardiovascular and cancer deaths.

In the participants alone, followed until the end of 1982 (Paper VI, table I), cancer was the leading contributor to the mortality (61 deaths) followed by alcohol-related (55) and coronary heart disease (CHD) deaths (50). Altogether, 218 deaths occurred in the participant group during the entire follow-up period.

2. Alcohol-related death

In order to estimate the role of alcohol as cause of death, a new death-cause category, "alcohol-related death" (ARD) was defined, in which group alcohol was considered the major (underlying) cause of death. The following mortality categories were included:

1. ACCIDENT in alcohol-intoxicated state,
almost always in known alcoholics,
2. SUICIDE in an alcoholic,
3. ORGANIC COMPLICATION. Organic complication to alcoholism in an alcoholic,
e.g. liver cirrhosis, pancreatitis and cardiomyopathy,
4. PNEUMONIA in an alcoholic,
5. CAUSE UNKNOWN in an alcoholic,

6. INTOXICATION. In this group were included:

Known alcoholics, found dead, with alcohol demonstrable at (forensic) necropsy and with no other demonstrable specific cause of death, such as myocardial infarction, cancer or cerebral haemorrhagia,

7. OTHER ALCOHOL-RELATED CAUSES OF DEATH, in alcoholics, such as death in delirium tremens.

The total numbers in these categories for the participants in paper VI are shown in table I. The classical indicator of alcohol abuse, liver cirrhosis, only accounted for 5 of the 55 alcohol-related deaths in this group, i.e. less than 10 per cent. The multitude of ways in which alcohol emerges as involved in death is evident from the table. The most common mode of ARD was "intoxication" (20 out of 55), followed by suicide (12 out of 55).

ALCOHOL-RELATED DEATHS (n = 55)	
Cause of death	No
Accident	5
Liver cirrhosis	5
Other organic	5
Suicide	12
Pneumonia	1
Cause unknown	3
Intoxication	20
Other	4
Total	55

Table I. Causes of death in the alcohol-related death (ARD) group (n=55), in the participants followed until end of 1982 (paper VI).

The heart-blood alcohol concentrations in a group of 45 subjects dead in "intoxication" are shown in paper V, fig 2. In three subjects, the alcohol was demonstrated in the urine only. Twenty subjects showed a heart-blood alcohol concentration of less than or equal to 2.0 per mille. Eleven subjects exceeded this level. The validity of the designation 'intoxication' death in many of these subjects can thus be questioned; a more reliable terminology would perhaps be 'sudden deaths in alcoholics'. In many of these subjects a combination of coronary atherosclerosis and alcohol intoxication was stated as cause of death in the autopsy protocols.

In order to illuminate the degree of coronary atherosclerosis in the intoxication subgroups of ARD, an assessment was made and compared with the CHD death group proper in the subjects of paper VI. The results of this analysis are shown in table II.

Degree of coronary atheromatosis	Cause of death	
	CHD	ARD/intoxications
	n=50	n=20
+++ , ++	37	2
+	3	17
0	1	1
Unknown	9	0
Thrombus	15	0
Total	50	20

Table II. Degree of coronary atheromatosis in coronary heart disease (CHD) deaths and in alcohol-related deaths(ARD)/intoxications. +++= occlusion, ++=severe narrowing, +=no narrowings, 0=no atheromatosis. CHD group: forensic autopsy - 30, autopsy in hospital - 14, no autopsy - 5. All ARD/intoxications were autopsied at the Forensic Department.

In the intoxication group, only 2 of 20 had coronary occlusive disease (+++) or severe narrowing (++). One of these subjects demonstrated a heart-blood alcohol concentration of 2.5 per mille and the other subject 0.4 per mille. There were no coronary thromboses. In the CHD group (n=50), data were obtained in 41 subjects, 37 of whom had occlusions (+++) or severe narrowing (++) in the coronaries.

A comparison with the official statistics was made for the group classified by us as alcohol-related deaths in paper IV, table I. In this analysis, which comprised both participants and non-participants, 61 out of 199 deaths (30.7%) were alcohol-related according to the previously defined criteria. In the official statistics, only 10 of these were retrieved with a definite statement of alcohol as the underlying cause of death; i.e. a proportion of about 1 out of 6. Even most of the liver cirrhosis cases in known alcoholics were not classified as alcohol-related in the death certificates.

The tendency of an underreporting of alcohol-related mortality in the official death cause statistics was supported by a calculation (Paper IV) of "excess" deaths in males with an alcohol-positive history and showing that these excess deaths corresponded to 39.2 per cent of all deaths. Said estimation thus indicates that the group 'alcohol-related deaths' - if anything - is an underrating of the 'true' role of alcohol for mortality.

3. Coronary heart disease death

In paper VI, 50 of 218 deaths in the participants were ascribed to coronary heart disease (CHD). Necropsy was performed in 44 of these subjects. The death certificate statement on the cause of death was followed, with the following exceptions:

1. One subject with the statement of cerebral haemorrhagia was changed to CHD as this seemed to be the initial event.
2. The subjects, which fulfilled the criteria for inclusion in the ARD group.

The degree of coronary atherosclerosis is shown in table 2 for 41 subjects. Four had moderate or no atheromatosis, and would accordingly seem to be misclassified.

Twenty-seven out of the 50 CHD deaths were diagnosed as myocardial infarction, and 23 as coronary heart disease deaths without firm evidence of myocardial infarction. A coronary thrombosis was present in 15 of the 27 myocardial infarctions, but in none of the others. Nineteen of the 23 deaths in CHD without myocardial infarction were sudden deaths (i.e. death within 24 hours of the onset of symptoms, or unwitnessed death), 1 died during surgery, and in 3 cases information was incomplete.

4. Suicides

In the participants (n=218), 25 of the deaths were ascribed to suicide (11.5%). Twelve of them were alcoholics and thus included in the group alcohol-related deaths; 13 lacked this history (Table III). Alcohol was demonstrated at necropsy in 13 subjects, 11 of whom were considered ARD.

SUICIDES (n = 25)			
Demonstration of alcohol at forensic autopsy	ARD	non-ARD	Total
+	11	2	13
-	0	9	9
Unknown	1	2	3
Total	12	13	25

Table III. Demonstration of alcohol in the body at forensic autopsy among suicide deaths in the participants, in relation to ARD/non-ARD category.

Since necropsy was performed in all cases of suicide, this means that demonstration of alcohol in the body at necropsy was a strong indicator that the subject in question also had a history of alcoholism.

The suicide modes are shown in table IV. Hanging was the most common (9 subjects) followed by fuel exhaust, i.e. carbon monoxide poisoning (6 subjects). Hanging was over-represented in the alcohol-related group and less frequent in the non-alcohol-related suicides. Drowning and shooting occurred only in the non-alcohol-related group while intoxication was more common in the alcohol-related suicides.

SUICIDES - METHODS OF DEATH			
Method of death	ARD	non-ARD	Total
Drowning	-	3	3
Shooting	-	2	2
Intoxication	4	1	5
Fuel exhaust	1	4	5
Hanging	7	2	9
Jumping	-	1	1
Total	12	13	25

Table IV. Methods of death among suicides (n=25) in participants (218 deaths; paper VI) in relation to ARD/non-ARD. ARD = alcohol-related death.

Since the non-participants were not included in the suicide analysis, the suicide group is probably larger than the present estimation. Some of the ARD-intoxications may have been suicides, even if the intent was unknown or undetected; three of them had drugs as well as alcohol demonstrated at necropsy and were referred to the ARD group since there were no farewell letters left of other circumstances speaking for suicide. In the alcohol intoxication deaths classified as suicide, this intent was documented by farewell letters. Two cases in the suicide group were unconfirmed as to intent but the circumstances were in favour of suicide; in one case by jumping from a window, and in the other case by drowning.

5. Cancer death

The cancer deaths by site in the updated participant group (n=218) are shown in table V. Cancer of the lung, stomach and pancreas accounted for 33 out of the 61 cancer deaths. Fourteen cancers were "early", i.e. they were probably present at the time of screening and in some subjects already known at screening, table VI. Only one of the subjects died within the first year after screening (11 months).

CANCER DEATHS	
Localization	No
Stomach	12
Oesophagus	1
Lung	12
Pancreas	9
Haematopoetic system	8
Colon - rectum	6
Brain	3
Liver	2
Other	8
Total	61

Table V. Cancer deaths (n=61) after screening in participants (218 deaths; paper VI).

"EARLY" CANCER DEATHS	
	No
Known at screening	4
Known before screening (in retrospect)	2
Diagnosed at screening	7
Death within one year after screening	1
Total	14

Table VI. "Early" cancer deaths, i.e. subjects with (probable) prevalent cancer already at the time of the screening (14 of 61 cancer deaths; see table V!).

The histologies in the lung cancer group (n=12) were: small-cell carcinoma, 7; adenocarcinoma, 2; undifferentiated carcinoma, 2; and squamous cell carcinoma, 1. The histology thus differed from what is generally expected (Stayner and Wegman 1983) by the low rate of squamous cell carcinoma. All lung cancer subjects were smokers, however, and 10 out of 12 dead subjects smoked more than 10 cigarettes per day.

Twelve subjects died from cancer of the stomach. Two of these had previously been operated for cancer of the stomach with Billroth-I (B-I) operation. Of the remaining 10 subjects, 5 had previously been operated with Billroth-II (B-II) operations for benign ulcer; 4 more than 20 years before death, and 1 five years before death. In the latter case the cancer was situated in the cardiac portion of the ventricle (adenocarcinoma).

This means a considerable over-representation of deaths from cancer of the stomach in males operated for benign ulcer with B-II operation in this population. In total, 260 subjects (3.3% of all participants) answered in the affirmative the question in the screening questionnaire: "Are you operated for gastric/duodenal ulcer?" It was found that not more than 140 of these could have been operated with a B-II operation, as judged from the distribution of these operations in the total control group (n=436, paper VI). The death rate in cancer of the stomach thus was 3.6% in the B-II operated group, compared with

0.07% in the non-operated part of the population, an increased incidence of more than 50 times.

This over-representation is much larger than previously reported (MacLean Ross et al. 1982, Logan and Langman 1983). It may be age-related, and is so large that screening measures might be indicated in this age group.

6. Intervention measures among the deceased subjects

This paragraph only intends to give a rough idea of the magnitude of intervention from the time of screening in the mortality group, and no attempt to evaluate the effects is made. Among the 218 participant subjects followed until the end of 1982, one or more interventive measures (excluding control of abnormal values performed by nurses, routine pulmonary X-rays in heavy smokers etc) were instituted in 79 (Table VII). Of these, 48 were enrolled in some form of continuous treatment at the Preventive Medicine out-patient clinics, 15 for hypertension, 21 for elevated blood lipids, 12 for elevated GGT level and 10 for borderline type II diabetes mellitus. Seven of the cancers who later died were detected at screening.

INTERVENTION AMONG MALES WHO DIED (n=218)	
Type of intervention	No
Hypertension clinic	15
Hyperlipidemia clinic	21
Intervention for heavy drinking	12
Borderline diabetes clinic	10
Referrals to hospital	2
Miscellaneous, including 7 detected cancers	19
Total	79

Table VII. Interventive measures among the dead participants (n=218). Rereferrals to house physicians and primary drop-outs are not included. Heavy drinkers were identified by means of elevated levels of GGT, and intervention randomized 1:1.

A more detailed description and discussion of possible intervention effects has been made in the case of the alcohol-related mortality in paper V. However, a more thorough general description and analysis of intervention is out of scope of this study. The predominant effect of the intervention would be to reduce the various trends of risk factors and determinants for premature mortality which constitute the primary subject of the present investigation.

7. Discussion

The most conspicuous finding in the present analysis of premature mortality in Malmö males around 50 years of age, is the prominent role of alcohol-related death, i.e. deaths in which alcohol was considered to be the underlying causative factor.

It is very difficult to assess the role of alcohol for death in single individuals. However, it is well known, that official statistics underestimate this role, both in Sweden (Bolander 1981) and abroad (Hackl 1980). Indirect methods are thus often used, such as calculations of the over-mortality of alcoholics in treatment programs (Schmidt and DeLint 1972, Sundby 1967, Thorarinsson 1979).

Another approach was attempted by Hackl (1980). He pointed out the inadequacy of liver cirrhosis deaths as a measure in this respect, a finding also corroborated in the present study, and instead examined the official statistics in Vienna for alcohol-labelled deaths (E 860, 303, 291 in the ICD classification), adjusting this figure upwards according to reports in the literature of over-mortality in alcoholics in different conditions. In this way he calculated that the mortality in the diagnoses in question ought to be multiplied by a factor of at least 29 to arrive at the true death rate due to alcohol.

The figure for alcohol-related deaths in the Malmö males in relation to the above diagnoses gives a multiplier of about 10 (61 compared with 6 in paper IV).

The official death coding requires that one cause of death be established. This is difficult in complex chains of events leading to death (Leiss 1982), and alcohol is often involved in such complex chains.

The most critical issue is whether the delineated group, ARD, is an exaggeration of the true role of alcohol for death. There are important reasons to believe that it is not. Firstly, an alcohol-positive history was required in nearly all cases. Secondly, a theoretical calculation of the excess deaths in the alcohol-positive group tended to support the view that this was still an underestimation. Moreover, no death in cancer or specific cardiovascular disease was classified as alcohol-related, although alcohol may be a contributory factor in these conditions (D'Alonzo and Pell 1968, Lieber et al. 1979).

The concept 'alcohol-related' has been used previously, but with varying implications. In the WHO report (Edwards et al. 1977) it was suggested that the term "alcohol-related disability" should indicate that "it is deemed to exist when there is an impairment in the physical, mental or social functioning of an individual, of such nature that it may be reasonably inferred that alcohol is part of the causal nexus determining that disability". This is a very 'wide' definition, difficult to use practically, and is not the one relied upon in this study.

Often, 'alcohol-related', implies certain parts of the official statistics with a degree of alcohol tinge, such as mentioning of alcohol in any place in the death certificate (Nashold and Naor 1981), or a combination of diagnoses that are considered to reflect alcohol effects, e.g. liver cirrhosis cum alcoholism (571.00), alcohol intoxication (E 860), alcoholism (291) and alcohol psychosis (303).

Apart from the fact that most cases of death due to liver cirrhosis are - wrongly - not even ascribed an alcoholic etiology, the present study supports previous findings that this disease comprises but a small part of the total alcohol-related deaths; less than 1/5 in the combined cohort of participants and non-participants described in paper V. As has been attempted here, the term 'alcohol-related' thus requires a definition of its use.

In the present investigation, suicide was a not uncommon cause of death. Half of the suicides (12 of 25) were alcohol-related according to the applied use of that term. This is probably a minimal estimate, since the alcohol-related deaths included some intoxications which may have been suicides. Bolander and Ettlinger (1980) have pointed out that the statistics on causes of death are unsatisfactory also as a basis for suicide research projects.

A further comment on the group ARD-intoxications is warranted. This large group demonstrates a rather uniform mode of death. The subjects, known alcoholics, were as a rule found dead in their apartments. It was unusual that the degree of alcohol intoxication as judged by the concentration in the heart blood at the forensic autopsy was high enough to explain the death from alcohol poisoning per se, i.e. by alcohol-induced depression of the respiratory center (Poikolainen 1977).

However, it is well known, that complications to alcohol abuse tend to occur in the abstinence phase, e.g. delirium tremens and cardiac arrhythmias (Ettinger et al. 1978). In some subjects in the ARD-intoxication group the death was ascribed to a concomitant coronary atherosclerosis. However, the degree of coronary involvement differed markedly in this category from the CHD deaths. It must be concluded that the described pattern of death is common in alcoholics, that it is related to the alcohol abuse and that the exact mechanism is unknown but it possibly might be due to a cardiomyopathy due to alcohol. This group may rather be labelled "sudden deaths in alcoholics" and may be equivalent with the one that has been designated "fatty liver-associated sudden death" (Randall 1980).

ENTRY CHARACTERISTICS IN RELATION TO MORTALITY

1. Non-participation (Paper V)

Non-participation (NP) is usually not considered as a screening variable, but is in fact an important one. The final figure for the participation (P) in the studied cohorts was 7,948 out of 10,353 invited, or 76.8 per cent. The death rate in the NP group was more than double as high as that in the P group. To the major part, the reason for this difference resided in the ARD category. The over-mortality in the other main death causes, viz cancer, cardiovascular and miscellaneous, was smaller and did not attain statistical significance.

Discussion

Many well-known epidemiological investigations, e.g. the Framingham (Dawber 1980), Kaiser Permanente (Klatsky et al. 1981) and Stockholm Prospective (Böttiger and Carlson 1982) studies do not include non-participants. These have, however, been analysed in the 1913 year's men population in Gothenburg by Tibblin (1965), who states that one of the main reasons for non-participation was "a negative attitude towards medical care". Wilhelmsen et al. (1976) found that total mortality was three times larger in the NP than in the P group and that also the prevalence of alcoholism was higher.

Non-participants are probably a heterogenous group. Some are probably not "true" NP.s (wrong addresses etc), some have obviously high morbidity (e.g. alcoholics and chronically ill patients under care) and some are perhaps very healthy. The NP group in epidemiological investigations needs further study and is probably especially important in an alcohol-preventive program.

2. Mortality in males with an alcohol-positive history (Paper IV)

In the analysis in paper IV it was found that the mortality in males with an APH was 6.9 times higher than that in the other males.

In the participants followed until the end of 1982 (Paper VI), 55 out of 218 dead subjects were registered at the Department of Alcohol Diseases (RAD) compared with 23 out of the 436 controls (ratio 4.8:1, table VIII). This corresponds to an over-mortality of 5.5 in the RAD as compared with the non-RAD males.

CAUSE OF DEATH	n	Registered at DAD	
		n	%
Cancer	61	4	6.6
Coronary heart disease	50	3	6.0
Alcohol-related	55	44	80.0
Other	53	4	6.6
Total mortality	218	55	25.2
Controls	436	23	5.3

Table VIII. Registration at the Department of Alcohol Diseases (DAD) in relation to the mortality in the participants, their living controls (two for each proband) and to different causes of death.

Table VIII also shows the RAD rate for the major subgroups of death. 80 per cent of the RAD were registered while for cancers, CHD deaths and other deaths a slight and non-significant over-registration was present compared with the controls.

Discussion

An over-mortality in cohorts of alcoholics in treatment programs is frequently reported and amounts to about a doubling of the expected death rate (Schmidt and DeLint 1972, Sundby 1967, Thorarinsson 1979). However, one previous study from Malmö (Dahlgren 1951) did not show excess mortality in alcoholics when the results were corrected for marital status. The reason for the much higher excess death rate in the alcoholics in the present study are probably several: only males were included, the age at death covers a range where alcohol toll is great and the study was undertaken in a strictly urban environment.

3. Entry characteristics and total mortality (Paper VI)

The screening variable that was most strongly associated with the total premature mortality in this population was GGT ($p < 0.0001$). Statistically significant

associations were also found for Mm-MAST-score, smoking, serum triglycerides, systolic blood pressure (all positive) and serum creatinine (negative). There were no correlations between the total mortality and serum cholesterol, diastolic blood pressure, A/I-weight or serum urate. In general, however, stronger correlations were found for the main subgroups of death than for the total mortality.

Discussion

It was found that there existed a distinctly differential risk factor pattern for the different main subgroups of death (Paper VI, table II), which caused the reduced or even vanishing association between the examined risk factors and total mortality in comparison with its major subgroups. It was therefore considered more relevant to describe and discuss the risk factor patterns for each of these separately.

4. Entry characteristics and alcohol-related death (Papers III, VI and VII)

There were statistically highly significant positive correlations of screening GGT ($p < 0.0001$) and Mm-MAST ($p < 0.0001$) to ARD, and also strong inverse correlations of serum cholesterol ($p = 0.0046$) and creatinine ($p < 0.0001$). There were no significant associations of alcohol abstention, smoking, serum triglycerides, systolic or diastolic blood pressure, A/I-weight or serum urate (Paper VI).

In the multivariate analysis, by means of Mantel's test (Paper VI, table III), it was shown that GGT and Mm-MAST-score were correlated to ARD independently of each other. The correlation of GGT persisted also after correction for marital status as well as for serum cholesterol and creatinine.

In a logistic risk function calculation including the variables GGT, Mm-MAST and serum creatinine, a certain improvement of the predictive power in comparison with each of these single risk factors was seen (Paper VI, fig 1 a and b).

The power of GGT, compared with Mm-MAST and a combination of GGT and Mm-MAST to correctly identify the subjects with alcohol-positive history in the mortality group was analysed in paper VII. With cut-off levels for GGT and Mm-MAST defined as ≥ 1.40 $\mu\text{kat/l}$ and ≥ 2 yes answers, respectively, the sensitivity for GGT was

0.53, the specificity 0.85 and the positive predictive value 0.68. For Mm-MAST the corresponding figures were 0.70, 0.69 and 0.47. The combination of GGT and Mm-MAST resulted in a positive predictive value of 0.55.

According to these results, GGT showed a better positive predictive power in this group and modality of risk than the questionnaire test as well as the combination of both. In the same paper it was demonstrated that Mm-MAST was more sensitive than GGT as an indicator of alcohol consumption categories in the average middle-aged males and the known alcoholics in the screening population.

Discussion

GGT was initially reported as an indicator of alcohol effects on the liver (Rollason et al. 1972, Rosalki and Rau 1972, Wu et al. 1976). Since then, many reports have confirmed its usefulness in this respect (Horner et al. 1979, Kristenson et al. 1980, Wiseman and Spencer-Peet 1977). The usefulness is increased by the fact that GGT does not seem to be elevated in acute intoxication (Dunbar et al. 1982, Gill et al. 1982, Schuckit and Griffiths 1982). The physiological role for GGT is not exactly clear, but the enzyme appears to be predominantly involved in the transport of amino acids over cell membranes (Meister 1974). The mechanism for the increase of GGT with alcohol consumption is probably enzyme induction in the liver (Gadeholt and Harris 1980, Teschke et al. 1983). In the study by Teschke et al. (1983), elevations both of liver GGT and alkaline phosphatases were found, but increase in the serum concentration for GGT alone. Consequently, an enzyme induction is not a sufficient explanation for the increase in serum level, but some sort of membrane effect, possibly an injury, seems to be required as well.

Drugs are also known to cause GGT elevation in serum, most notably phenantoin barbiturates (Rosalki et al. 1971). Furthermore, GGT may be elevated in certain disease states, such as rheumatoid arthritis (Spooner et al. 1982) and hyperthyroidism (Azizi 1982), and it has likewise been associated with liver involvement in cancer (Aronsen et al. 1970).

In the present study, GGT was a strong risk factor for alcohol-related mortality, both singly and in combination with other markers. When indicating alcohol consumption levels, Mm-MAST was more sensitive in most of the examined groups of the screening population. This was particularly true in the known alcoholics, and this supports the argument that GGT is not a sufficient test for screening of alcoholism (Penn and Worthington 1983). For this purpose, a questionnaire is more sensitive, but the problem with this method is the high frequency of false positives; in our screening population almost 30 per cent responded in the affirmative to two or more of the Mm-MAST questions (Papers VI and VII).

We have primarily investigated and utilized GGT as a risk factor for alcohol-related health complications. In the ARD end-point, GGT was the strongest risk factor, but also Mm-MAST and, inversely, serum creatinine and cholesterol exhibited similar associations. The negative correlation between ARD and serum creatinine has in fact been described previously (Chan-Yeung et al. 1980, Gill et al. 1982) and has been reported also for serum urea (*idem*). As it is observed already in acute experiments (Gill et al. 1982), it may be due to a renal effect, but the precise mechanism has not been elucidated. A hormonal disturbance might be operating by way of a low androgen level in alcoholics (Wälimäki and Ylikahri 1981) and a consequently lower muscle mass or rate of creatinine synthesis.

In paper I it was found that the teetotallers showed the highest serum creatinine levels and the alcohol-positive high GGT group the lowest. The inverse correlation between serum creatinine and alcohol-related health disturbances would accordingly seem to reflect a continuous effect. In contrast, many "classical" alcohol indicators, like blood pressure, serum urate and triglycerides were more confined to the initial health screening findings (Papers I and II), but failed as risk indicators of ARD (Paper VI). These differences are probably due to the fact that early and advanced stages of alcohol-related disorders in many respects are in opposite metabolic and nutritional situations (Paper VI).

The same would seem to apply for the serum cholesterol findings. However, the strong inverse correlation between serum cholesterol and ARD has not been reported before. It was also shown that the group ARD-intoxications had a relatively low degree of coronary atherosclerosis (Table II). In paper I, a positive correlation between GGT and serum cholesterol was found, and previous reports likewise indicate a positive correlation (Grande and Amatuzio 1960,

Ostrander et al. 1974) or no correlation at all (Belfrage et al. 1977, Castelli et al. 1977) between serum cholesterol and alcohol consumption. Part of the explanation of these disparate findings may reside in the supposedly anti-atherogenic high density lipoprotein cholesterol fraction (Castelli et al. 1977, Ekman et al. 1981, Johansson and Medhus 1974), which was not measured in the present study.

5. Alcohol abstention and mortality (Paper VIII)

The mortality in relation to Mm-MAST score results is represented in paper VIII, table II, and fig 2 below.

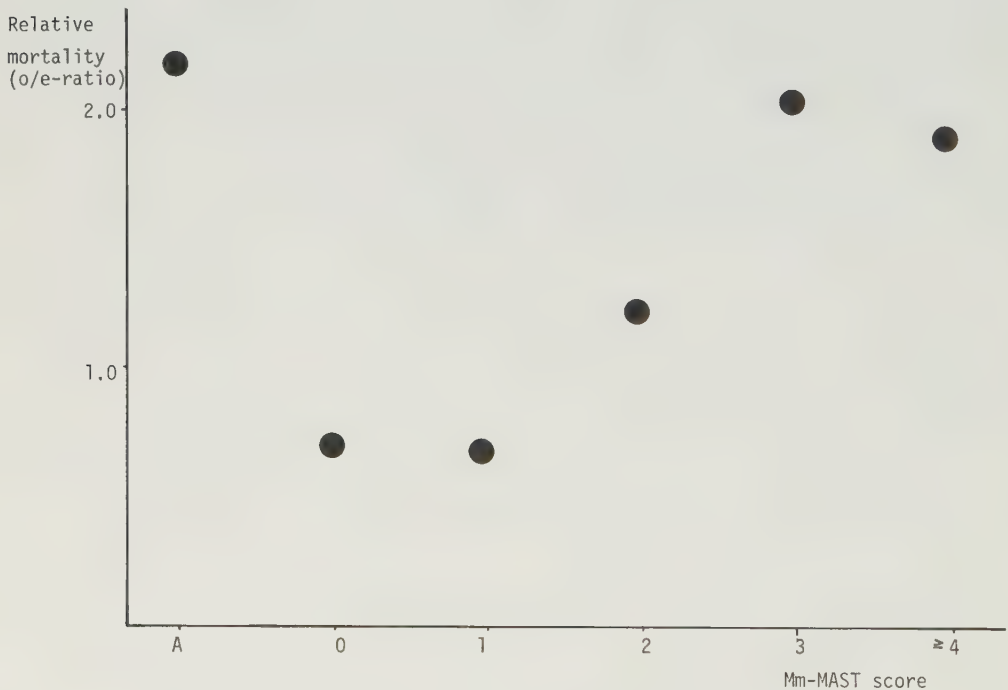


Fig. 2. Distribution of men who died (n=82) among six categories of reported attitudes to alcohol consumption, Mm-MAST score, in relation to the distribution of a control group (n=155). Data from table II, paper VIII. A = alcohol abstention.

The relative mortality was lowest for 0-1-scorers, and showed an almost linear increase for 2-, 3- and 4-scorers. The self-reported teetotallers' mortality was in the same range as the 3- 4-scorers, and a U-formed relationship was thus found.

A further analysis of these findings is hampered by the small numbers in the respective score categories. In the control group, 6 subjects out of 255 reported themselves as abstainers (4.0%) in comparison with 7 of 55 deceased subjects (8.5%). When the latter subjects were analysed it was found that 4 of the 7 - at the time of the screening - suffered from severe chronic disease; one was a chronic alcoholic, one suffered from chronic hepatitis, one from epilepsy and one from severe rheumatoid arthritis.

The proportion of alcohol-related deaths in the different Mm-MAST-score categories is shown in paper VIII, table III. This again shows a U-formed relationship with the lowest proportion of alcohol-related deaths in the 0-score category, higher proportion in the self-asserted alcohol abstainers and a pronounced increase in the higher score range. Out of 8 deaths with a score result of >4 , 7 were alcohol-related.

Discussion

The small numbers in this study preclude firm conclusions. The over-mortality in self-stated abstainers may be due to a higher proportion of alcoholics and otherwise chronically ill people who for that reason have quitted alcohol consumption. These findings cast doubt over studies which ascribe an excess mortality to abstainers as due to their abstention (Blackwelder et al. 1980, Cullen et al. 1982, Klatsky et al. 1981, Marmot et al. 1981). It is probably unwise to include teetotallers in alcohol consumption categories, as this group may have special characteristics (Barboriak et al. 1979, Klatsky et al. 1981).

6. Entry characteristics in relation to death in coronary heart disease

(Papers VI and IX)

Significant correlations to death in coronary heart disease were - as expected - found for smoking ($p=0.0062$), serum cholesterol ($p=0.00014$), triglycerides

($p=0.00013$), systolic blood pressure ($p=0.000012$), diastolic blood pressure ($p=0.0021$) and GGT ($p=0.034$).

There were no correlations to alcohol abstention, Mm-MAST-score, serum urate or A/I-weight.

The multivariate analysis by Mantel's test showed that GGT was no longer of independent importance when either serum cholesterol or systolic blood pressure were taken into account (Paper VI, table III). There was no independent role for diastolic blood pressure ($p > 0.30$) when systolic blood pressure was analysed as the foreground variable. However, both serum cholesterol and triglycerides contributed independently to the risk (Paper VI, table III).

The separate risk functions under order restriction of serum cholesterol, triglycerides, systolic blood pressure and smoking in relation to CHD death are presented in paper VI, fig 2 a-b; and a logistic risk function with the same variables in fig 2 c. The latter risk function was more powerful than the separate risk estimations as expressed by its curve initially lying below the curves of the others, than intersecting and finally, in the region of the eight decedentile of risk, surpassing them.

Discussion

According to Stamler (1980), there existed 28 prospective epidemiological studies by mid -80 showing a significant correlation between serum cholesterol and CHD. Stamler calls it "an established relationship" (idem). The present study thus documents this finding once more, and also the well-known importance of smoking for CHD.

The result that the systolic blood pressure was of greater importance for CHD risk than the diastolic has been reported previously (Kannel 1976). However, the total lack of importance of diastolic blood pressure in the multivariate analysis was surprising. If this reflects the biological truth or if some other explanation may be advanced is unclear. It is annoying, however, that in daily clinical practice the diastolic blood pressure is almost exclusively relied upon.

The present investigation is at variance with the view that serum triglyceride does not constitute an independent risk factor for CHD (Hulley et al. 1980).

However, the Stockholm Prospective Study found triglyceride to be strongly associated with risk for coronary heart disease, but on the other hand failed to confirm the association of serum cholesterol (Böttiger and Carlson 1980).

GGT was positively correlated to CHD death in the univariate analysis but this association disappeared when either serum cholesterol or systolic blood pressure was taken into account. This does not exclude the operation of a common factor, such as alcohol, raising both GGT, serum cholesterol and systolic blood pressure. However, no consistent relationship between alcohol and CHD death could be identified in the study. There was a statistically significant inverse correlation between serum cholesterol and alcohol-related death implying that these, probably advanced, alcoholics might have had less coronary atherosclerosis than at least the CHD subjects. Moreover, there was no over-representation of CHD deaths in the RAD group compared with the control group.

The data in the present report support previous observations that advanced alcoholics may have a low degree of coronary atherosclerosis (Cabot 1904). However, the dose of alcohol which may still be compatible with health for the coronaries may possibly be too high for the myocardium and henceforth contribute to the great share of sudden deaths in alcoholics. Neither was it possible to substantiate an increased frequency of coronary events in the alcohol abstainers. One could rather imagine that even a moderate alcohol abuse would tend to be unfavourable to the coronary arteries as it seems to elevate serum cholesterol, triglycerides and blood pressure, in contrast to the situation in advanced alcoholics. However, since high density lipoprotein cholesterol was not measured in the study, no definite conclusions can be made. The results in any case do not confirm the view that there exists a level of alcohol consumption which is healthy for the coronary arteries and protective against coronary heart disease (Blackwelder et al. 1980).

7. Entry characteristics and cancer death (Papers VI, IX and X)

An inverse correlation, statistically significant by trend analysis, between serum cholesterol at screening and a group of 44 subsequent cancer deaths was described in paper IX. In a comparison by Fisher's test in 61 cancer deaths in paper VI, the same tendency was seen, albeit with a lower statistical significance ($p=0.056$). However, when a statistical analysis with test for trend was performed

in this group significance was reached ($p=0.03$), and persisted also after exclusion of the cancers that were probably present already at the screening.

A positive correlation of cancer death and serum urate was found in the trend analysis in paper X ($p<0.01$) and in the analysis in paper VI with Fisher's test ($p=0.0023$). In the former analysis this association was confined to the cancer deaths occurring ≤ 2.5 years after screening.

The numbers were too small to identify significant tendencies of associations for specific cancer sites.

Smoking did not reach statistical significance ($p=0.072$) in relation to the whole cancer mortality group (Paper VI). However, all 12 subjects that died in lung cancer were smokers.

There were no associations to cancer deaths for GGT or any of the other screening variables. A tendency to an over-representation of cancers in the abstainers was, however, present ($p=0.064$, paper VI).

Discussion

The finding in this study of an inverse correlation of serum cholesterol and cancer has been reported in several previous studies (Beaglehole et al. 1980, Cambien et al. 1980, Garcia-Palmieri et al. 1981, Kark et al. 1980, Kozarevic et al. 1981, Rose et al. 1974, Williams et al. 1981). It has mainly been documented in males, and there is no agreement as to the types of cancers involved. It has mostly been interpreted as an early sign of cancer (Cambien et al. 1980, International Collaborative Group 1982, Rose and Shipley 1980). Alternatively, it has been suggested that the association is secondary to a low serum level of vitamin A (Kark et al. 1982). That it might be a sign of an early and undetected malignancy in at least a fraction of the cases is also supported by the common clinical experience that the occurrence of severe disease, such as rheumatoid arthritis or after a myocardial infarction, is associated with lowering of the serum cholesterol levels.

However, in the present study the inverse relationship persisted in the cases dying also within 2.5-6 years after the screening, why it is possible that the

development of cancer in some cases may have been related to the state of low cholesterol (Paper IX).

The positive association of serum urate and cancer was unexpected. It has even been suggested that serum urate might provide an anti-oxidant protection against cancer (Ames et al. 1981). The association was only found for "early" cancers in the analysis in paper X.

The fact that the constellation of elevated serum urate and lowered serum cholesterol was predominantly associated with the "early" cancers does not mean that these findings lack significance. It is difficult to fully explain them as secondary to an already established but otherwise occult tumour process alone. It could, at least in a proportion of the cases, reflect a "pre-malignant" state, maybe secondary to a carcinogenic stimulus with (generalized or localized) increased cell turn-over.

Obviously, the numbers in the group in the present investigation are small, and the findings chiefly underline the need for longer follow-up times and larger study groups as well as longitudinal examinations of intra-individual changes in serum urate and cholesterol levels. Such studies are under way.

There was no correlation between GGT and cancer death. This is slightly surprising, as GGT has been reported to be a sensitive indicator of liver involvement in cancer (Aronsen et al. 1970). However, this involvement mostly occurs so close to death that such individuals probably do not respond to an invitation to a screening investigation. Nevertheless, a pronouncedly elevated GGT value must be investigated for malignancy, and in fact one case of hepatic cancer and one case of pancreatic cancer were detected in this way.

As previously discussed, 5 of the 12 stomach cancers were previously operated by the Billroth II method. It is well known that there is an increased risk for gastric malignancy in this group, but in the present study this overrisk was very large; 50 times in comparison with un-operated subjects. This may justify a consideration of an elective preventive program.

Otherwise, gastric cancer has greatly reduced its incidence since several decades (Logan and Langman 1983) whereas most other cancers have remained rather constant. Furthermore, it has recently been stated that "our two main enemies, cancer and ischemic heart disease are both essentially avoidable" by analogous means, "which have not yet been fully implemented" (Doll 1983), and this makes a further search and identification of general and individual prospective risk factors for cancer all the more important.

CONCLUDING REMARKS

Some hold to the convention that no new hard facts not earlier presented should be allowed in discussion and concluding remarks. To the contrary, it is the opinion of the present author that the tools for evaluating alcohol-related deaths and the predictors for this outcome should be reevaluated as frequently as possible. This applies particularly to all parameters easily obtainable in everyday examinations. Therefore, a few examples of this are shortly touched on below.

It is a truism to state that the results in this study only apply to this particular population, i.e. middle-aged urban males who died early at an average age of about 50 years. These findings cannot be unjudiciously extrapolated to other ages, geographical environments or to women. This caution seems especially crucial when applied to the role of alcohol for death.

Another truism: the use of GGT in the tracing of high alcohol consumers is only to be regarded as an enrichment process. No elevated GGT value can be taken as indicative of high alcohol consumption unless further penetratingly evaluated. Several other ways might lead to a careful penetration of alcohol habits. Such ways have been indicated in paper VI, in which it was shown that there was correlation between alcohol-related death and the response to the questionnaire, Mm-MAST, and also inversely with serum creatinine.

Therefore a few distribution diagrams are shown that point to the other possibilities that open up in this area. Fig 3 shows the distribution for Mm-MAST score versus serum GGT for the ARD:s and their controls (two for each proband), and fig 4 shows the distribution for Mm-MAST versus serum creatinine.

Fig 5 shows the distribution of serum GGT versus serum creatinine. These figures indicate that the various combinations of these variables may increase the enrichment. This seems especially so when looking at the distribution of ARD:s in the diagram where serum creatinine is plotted against serum GGT.

This question must be pursued further by analysing not only the deaths but also some other hard end-points for high alcohol consumption such as hospital admission for severe organic damage, repeated entrance to alcohol institutions or other such data, versus the given distributions.

Mm-MAST
score ≥ 4

3

2

1

0

A

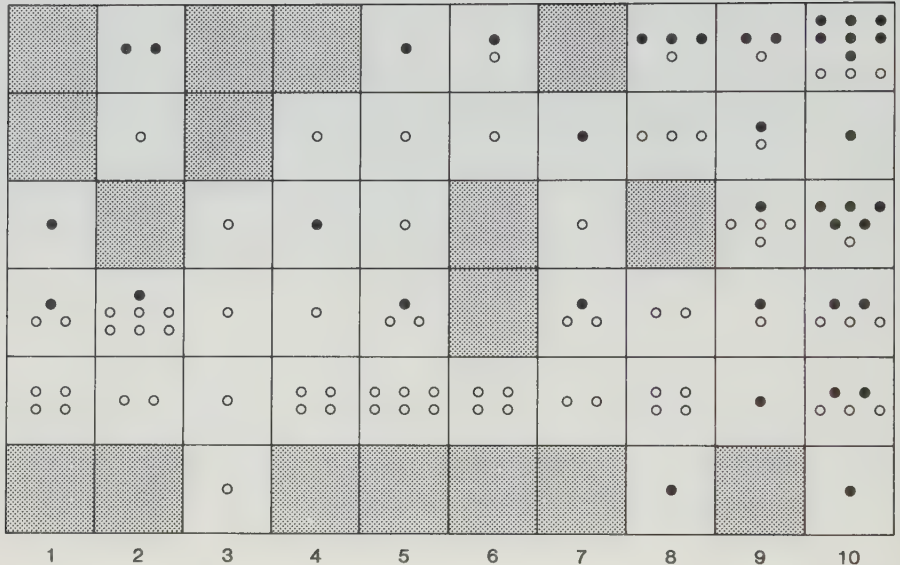


Fig. 3

GGT deciles

Mm-MAST

score

 ≥ 4

3

2

1

0

A

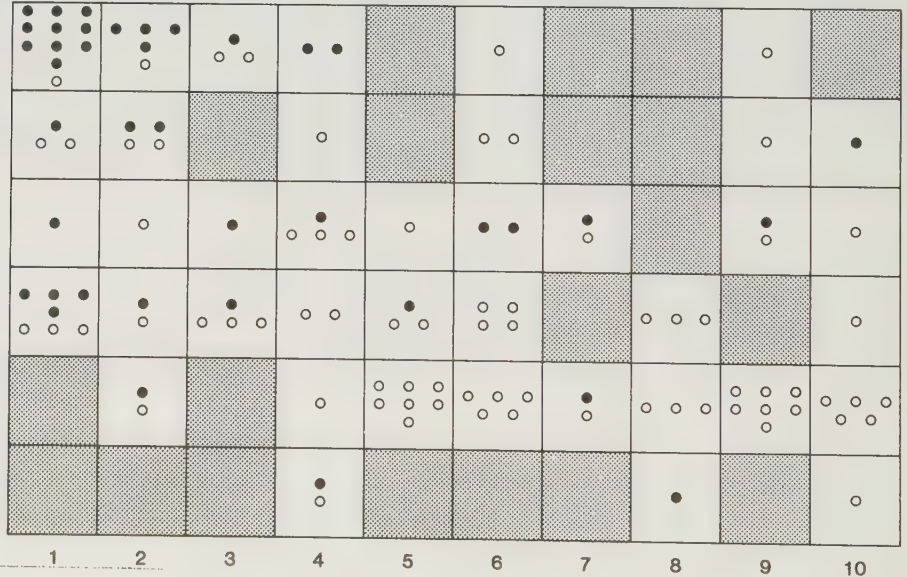


Fig. 4

Serum creatinine deciles

Fig. 3-4. Distributions of Mm-MAST score versus GGT (fig. 3) and serum creatinine (fig. 4) for ARD:s and their controls (study group from paper VI).

Serum creatinine decentiles

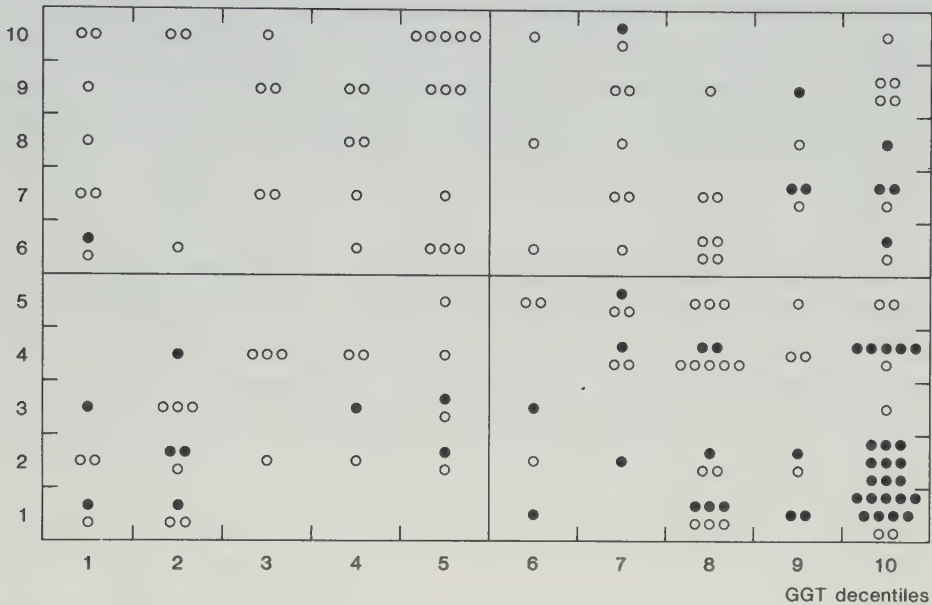


Fig. 5. Distribution of serum creatinine versus GGT for the ARD group and their controls (study group from paper VI).

Both high and low serum uric acid levels as well as both high and low serum triglyceride levels and low serum cholesterol are seen in the alcohol-related deaths. Without a penetrating longitudinal study on the shifts in these various laboratory parameters in a progressive course of high alcohol consumption from early stages it is difficult to pursue this line of argument any further.

There is, however, no doubt that various everyday routine laboratory examinations coupled with a simple attitude-oriented questionnaire, as the Mm-MAST, and with appropriate liver enzymes, would be useful in handing the physician probes for tactful and thorough penetration into a sensitive but outstanding for the future health of the individual.

The figure 30.7% of the deaths being referred to the alcohol-related group is shockingly high, even to the author. Therefore all these subjects have been worked through repeated times. Even if those with the criteria that may look a little bit less rigid than the others would be deleted, i.e. pneumonia or cause unknown in an alcoholic, this would only eliminate 5 out of 61 deaths in paper IV. The percentage alcohol-related deaths would then instead be 28.1%.

Working through the deaths which were listed as 'cardiovascular' and 'miscellaneous', in paper VI another 11 subjects are given in table IX who either had an alcohol-positive history or where alcohol could be demonstrated in the body at autopsy, but who did not fulfill the criteria for inclusion in the category 'alcohol-related deaths'. Using somewhat less rigid criteria, with inclusion of some of these, would result in an even higher share for the ARD:s of the total mortality.

That the observed patterns are genuine and valid is supported by the findings in the CHD mortality group, which were in good agreement with previous reports. They thus do not require any further comments here. However, they would also seem to corroborate that the trends observed in the neoplastic death cause group were relevant. Even though these were less pronounced than in the other major mortality categories, they clearly warrant further elucidation in future studies.

ALCOHOL BACKGROUND	ALCOHOL (%) AT AUTOPSY	CAUSE OF DEATH
1. APH (raised screening GGT [§])	-	Train accident (engine driver)
2. APH (RAD)	-	Tracheobronchitis
3. -	1.5 (blood)	Suicide
4. Probable APH (police report)	-	Probable suicide
5. APH (RAD)	-	Unclear, diabetes?
6. APH (hospital records)	-	Pneumonia
7. APH (police protocol)	-	Oesophagitis
8. APH (police protocol)	-	Tromboembolia pulm.
9. APH (RAD)	-	Cerebral haemorrhage
10. -	0.9 (blood)	Tromboembolia pulm.
11. -	0.7 (kidney)	Drowning (epileptic)

§ evaluated at interview as alcohol-induced

Table IX. Males with an alcohol-positive history (APH) or with alcohol demonstrable in the body at autopsy, but not included in the ARD category (study group from paper VI; 218 deaths). RAD = registration at the Department of Alcohol Diseases.

ACKNOWLEDGEMENTS

I am sincerely indebted to

Professor Bertil Hood, who initiated this work, and who has continuously generated ideas during its progress,

Associate Professor Erik Trell, for enthusiastic partnership; without whom this work had not been possible,

Kajsa Christensson, the secretary of this project, for careful secretarial work,

Associate Professor Mats Ekberg, head of the Department of Internal Medicine, Håssleholm's Hospital, and my other colleagues there, for continuous support,

The staff of the Department for Preventive Medicine for support of the project,

Professor Nils H. Sternby, Department of Pathology, and Professor Gerhard Voigt, Department of Forensic Medicine, Lund University, Malmö General Hospital, for supply of records and advice,

Anne-Marie Bolander, National Central Bureau of Statistics, for helpful counselling,

Anders Odén, Kungälv, for statistical analysis,

Margareta Nyberg for skilful typing of the work.

The studies were supported by the Swedish Council for Planning and Coordination of Research (Forskningsrådsnämnden), AFA (Arbetsmarknadens Försäkringsaktiebolag), and Kristianstads Läns Landsting.

REFERENCES

- d'Alonzo CA, Pell S. Cardiovascular disease among problem drinkers. *J Occup Med* 1968; 10:344-350.
- Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: A hypothesis. *Proc Natl Acad Sci USA* 1981;78:6858-6862.
- Armitage P. Statistical methods in medical research. Blackwell Scientific Publications, London 1971.
- Aronsen KF, Nosslin B, Pihl B. The value of gamma- glutamyl transpeptidase as a screen test for liver tumor. *Acta Chir Scand* 1970;136:17-22.
- Azizi F. Gamma-glutamyl transpeptidase levels in thyriod disease. *Arch Intern Med* 1982;142:79-81.
- Barboriak JJ, Anderson AJ, Hoffman RG. Interrelationships between coronary artery occlusion, high-density lipoprotein cholesterol, and alcohol intake. *J Lab Clin Med* 1979;94:348-353.
- Barlow RE, Bartholomew DJ, Bremner JM, Brunk HD. Statistical inference under order restrictions. Wiley, New York 1972.
- Beaglehole R, Foulkes MA, Prior IAM, Eyles EF. Cholesterol and mortality in New Zealand Maoris. *Br Med J* 1980;280:285-287.
- Belfrage P, Berg B, Hägerstrand I, Nilsson-Ehle P, Tornqvist H, Wiebe T. Alterations of lipid metabolism in healthy volunteers during long-term ethanol intake. *Eur J Clin Invest* 1977;7:127-131.
- Blackwelder WC, Yano K, Rhoads GG, Kagan A, Gordon T, Palesch Y. Alcohol and mortality: The Honolulu heart study. *Am J Med* 1980;68:164-169.
- Bolander A-M. Mortality as indicator of health at present and in a long-term perspective. *Health and Society:V:Different aspects of mortality in Sweden*. Forskningsrådsnämnden, Stockholm 1980.
- Bolander A-M, Ettlinger R. Suicide in Sweden. *Health and Society:V:Different aspects of mortality in Sweden*. Forskningsrådsnämnden, Stockholm 1980.

- Bolander A-M. Mortality statistics in Sweden and its neighbouring countries. Skandia International Symposia: Medical aspects of mortality statistics, Almqvist & Wiksell, Stockholm, 1981: pp 236-255.
- Bradley JV. Distribution-free statistical tests. Prentice-Hall, Englewood Cliffs, N.J. 1968.
- Böttiger LE, Carlson LA. Risk factors for ischaemic vascular death for men in the Stockholm Prospective Study. *Atherosclerosis* 1980;36:389-408.
- Böttiger LE, Carlson LA. Risk factors for death for males and females. A study of the death pattern in the Stockholm Prospective Study. *Acta Med Scand* 1982;211:437-442.
- Cabot RC. The relation of alcohol to arteriosclerosis. *JAMA* 1904;43:774-775.
- Cambien F, Ducimetriere P, Richard J. Total serum cholesterol and cancer mortality in a middle-aged male population. *Am J Epidemiol* 1980;112:388-394.
- Castelli WP, Gordon T, Hjortland MC, Kagan A, Doyle JT, Hames CG, Hulley SB, Zukel WJ. Alcohol and blood lipids. The Cooperative Lipoprotein Phenotyping Study. *Lancet* 1977;2:153-155.
- Chan-Yeung M, Ferreira P, Frohlich J, Schulzer M, Tan F. The effects of age, smoking, and alcohol on routine laboratory tests. *Am J Clin Pathol* 1981;75: 320-326.
- Cramér H. Mathematical methods of statistics. Princeton University Press, 1946.
- Cullen K, Stenhouse NS, Wearne KL. Alcohol and mortality in the Busselton Study. *Int J Epidemiol* 1982;11:67-70.
- Dahlgren KG. On death-rates and causes of death in alcohol addicts. *Acta Psychiatr Neurol Scand* 1951;XXVI:297-311.
- Dawber TR. The Framingham Study. The epidemiology of atherosclerotic disease. Harvard University Press, Cambridge, Massachusetts 1980.
- Doll R. Prospects for prevention. *Br Med J* 1983;286:445-453.
- Dunbar JA, Hagart J, Martin B, Ogston S, Devgun MS. Drivers, binge drinking, and gammaglutamyltranspeptidase. *Br Med J* 1982;285:1083.
- Edwards G, Gross MM, Keller M, Moser J, Room R. Eds. Alcohol-related disabilities. WHO Offset Publication No. 32, WHO, Geneva 1977.

- Ekman R, Fex G, Johansson BG, Nilsson-Ehle P, Wadstein J. Changes in plasma high density lipoproteins and lipolytic enzymes after long-term, heavy ethanol consumption. *Scand J Clin Lab Invest* 1981;41:709-715.
- Ettinger PO, Wu CF, de la Cruz C, Weisse AB, Ahmed SS, Regan TJ. Arrhythmias and the "holiday heart": alcohol-associated cardiac rhythm disorders. *Am Heart J* 1978;95:555-562.
- Fox AJ, Ebeling K, Eklund G, Pettersson BF, Hakama MK, Harvei S, Ingimarsson S, Mehnert WH, Péter Z, Staszewski J, Trell E, Wagner G. The role of epidemiology in cancer control. Report on a WHO meeting, Lyon 2-4 November 1982.
- Gadeholt G, Aarbakke J, Dybing E, Sjöblom M, Mörlund J. Hepatic microsomal drug metabolism, glutamyl transferase activity and in vivo antipyrine half-life in rats chronically fed an ethanol diet, a control diet and a Chow diet. *J Pharmacol Exp Therap* 1980;213:196-203.
- Galen RS, Gambino SR. Beyond normality. The predictive value and efficiency of medical diagnoses. John Wiley, New York 1975.
- Garcia-Palmieri MR, Sorlie PD, Costas R, Havlik RJ. An apparent inverse relationship between serum cholesterol and cancer mortality in Puerto Rico. *Am J Epidemiol* 1981;114:29-40.
- Gill GV, Baylis PH, Flear CTG, Skillen AW, Diggle PH. Acute biochemical responses to moderate beer drinking. *Br Med J* 1982;285:1770-1773.
- Goldacre MJ, Harris RI. Mortality, morbidity, resource allocation, and planning: a consideration of disease classification. *Br Med J* 1980;281:1515-1519.
- Grande F, Amatuzio DS. The influence of ethanol on serum cholesterol concentration. *Minnesota Medicine* 1960;731-735.
- Hackl H. Untersuchungen zur Ermittlung der wahren Alkoholismus-Sterblichkeit. *Dtsch med Wschr* 1980;105:1743-1747.
- Horner F, Kellen JA, Kingstone E, Maharaj N, Malkin A. Dynamic changes of serum gamma-glutamyl transferase in chronic alcoholism. *Enzyme* 1979;24:217-223.
- Hulley SB, Rosenman RH, Bawol RD, Brand RJ. Epidemiology as a guide to clinical decisions: the association between triglyceride and coronary heart disease. *N Engl J Med* 1980;302:1383-1389.
- ICD-International Classification of Disease. Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death (1965), WHO 1967.

- International Collaborative Group. Circulating cholesterol level and risk of death from cancer in men aged 40 to 69 years. *JAMA* 1982;248:2853-2859.
- Janzon L, Lindell Sven-Erik, Trell E. Smoking and disease. Attitudes and knowledge in middle-aged men. *Scand J Soc Med* 1981;9:127-133.
- Johansson BG, Medhus A. Increase in plasma alpha-lipoproteins in chronic alcoholics after acute abuse. *Acta Med Scand* 1974;195:273-277.
- Kannel WB. Some lessons in cardiovascular epidemiology from Framingham. *Am J Cardiol* 1976;37:269-282.
- Kark JD, Smith AH, Hames CG. The relationship of serum cholesterol to the incidence of cancer in Evans County, Georgia. *J Chron Dis* 1980;33:311-322.
- Kark JD, Smith AH, Hames CG. Serum retinol and the inverse relationship between serum cholesterol and cancer. *Br Med J* 1982;284:152-154.
- Keller M. A lexicon of disablements related to alcohol consumption. In: Edwards G, et al, eds. Alcohol-related disabilities. WHO Offset Publication No. 32, WHO, Geneva 1977.
- Keys A. Seven Countries. A multivariate analysis of death and coronary heart disease. Harvard University Press, Cambridge, Massachusetts 1980.
- Klatsky AR, Friedman GD, Siegel AB. Alcohol and mortality. A ten-year Kaiser-Permanente experience. *Ann Intern Med* 1981;95:139-145.
- Kozarevic D, McGee D, Vojvodic N, Gordon T, Racic Z, Zukel W, Dawber T. Serum cholesterol and mortality. The Yugoslavia Cardiovascular Disease Study. *Am J Epidemiol* 1981;114:21-28.
- Kristenson H, Trell E, Fex G, Hood B. Serum gamma-glutamyltransferase: statistical distribution in a middle-aged male population and evaluation of alcohol habits in individuals with elevated levels. *Prev Med* 1980;9:108-119.
- Kristenson H. Studies on alcohol related disabilities in a medical intervention programme in middle-aged males. Thesis, Malmö 1982.
- Kristenson H, Trell E. Indicators of alcohol consumption. Comparisons between a questionnaire (Mm-MAST), interviews and serum-gamma-glutamyltransferase (GGT) in a health survey of middle-aged males. *Br J Addict* 1982;77:297-305.
- Leiss J. Die Todesursache unter individual-pathologischen Gesichtspunkten. *Dtsch med Wschr* 1982;107:1069-1072.

- Lieber CS, Seitz HK, Garro AJ, Worner TM. Alcohol-related diseases and carcinogenesis. *Cancer Res* 1979;39:2863-2886.
- Lindberg W, Natvig H, Rygh A, Svendsen K. Høyde og vekstundersøkelser hos voksne menn og kvinner. *Tidsskr Norsk Lægeforen* 1956;76:361-371.
- Logan RFA, Langman MJS. Screening for gastric cancer after gastric surgery. *Lancet* 1983;2:667-670.
- Mantel N. Chi-square tests with one degree of freedom: Extensions of the Mantel-Haenszel procedure. *J Am Stat Assoc* 1963;58:690-700.
- Marmot G, Shipley MJ, Rose G, Thomas BJ. Alcohol and mortality: a U-shaped curve. *Lancet* 1981;1:580-583.
- McLean Ross AH, Smith MA, Anderson JR, Small WP. Late mortality after surgery for peptic ulcer. *N Engl J Med* 1982;307:519-522.
- Meister A. The gamma-glutamyl cycle. Diseases associated with specific enzyme deficiencies. *Ann Intern Med* 1974;81:247-253.
- Nashold RD, Naor EM. Alcohol-related deaths in Wisconsin: the impact of alcohol on mortality. *Am J Publ Health* 1981;71:1237-1241.
- Ostrander LD, Lamphiear DE, Block WD, Johnson BC, Ravenscroft C, Epstein FH. Relationship of serum lipid concentrations to alcohol consumption. *Arch Intern Med* 1974;134:451-456.
- Penn R, Worthington DJ. Is serum gamma-glutamyltransferase a misleading test? *Br Med J* 1983;286:531-535.
- Poikolainen K. Alcohol poisoning mortality in four Nordic Countries. The Finnish Foundation for Alcohol Studies, Helsinki 1977.
- Randall B. Sudden death and hepatic fatty metamorphosis. A North Carolina Survey. *JAMA* 1980;243:1723-1725.
- Rollason JG, Pincherle G, Robinson D. Serum gamma glutamyl transpeptidase in relation to alcohol consumption. *Clin Chim Acta* 1972;39:75-80.
- Rosalki SB, Rau D. Serum gamma-glutamyl transpeptidase activity in alcoholism. *Clin Chim Acta* 1972;39:41-47.
- Rosalki SB, Tarlow D, Rau D. Plasma gamma glutamyl transpeptidase elevation in patients receiving enzyme-inducing drugs. *Lancet* 1971;2:376-377.

- Rose G, Blackburn H, Keys A, Taylor HL, Kannel WB, Oglesby P, Reid DD, Stamler J. Colon cancer and blood-cholesterol. *Lancet* 1974;1:181-183.
- Rose G, Shipley MJ. Plasma lipids and mortality: a source of error. *Lancet* 1980;1:523-526.
- Scandinavian Enzyme Committee. Recommended method for the determination of gamma-glutamyltransferase in blood. *Scand J Clin Lab Invest* 1976;36:119-125.
- Schmidt W, deLint J. Causes of death of alcoholics. *Quart J Stud Alc* 1972;33:171-185.
- Schuckit MA, Griffiths JC. Gamma-glutamyltransferase values in nonalcoholic drinking men. *Am J Psychiatry* 1982;139(2):227-228.
- Spooner RJ, Smith DH, Bedford D, Beck PR. Serum gamma-glutamyltransferase and alkaline phosphatase in rheumatoid arthritis. *J Clin Pathol* 1982;35:638-641.
- SPRI-rapport Nr 122. Dödsorsaksstatistik - ett underlag för planering. SPRI, Stockholm 1983.
- Stamler J. The established relationship among diet, serum cholesterol and coronary heart disease. *Acta Med Scand* 1980;207:433-446.
- Stayner LT, Wegman DH. Smoking, occupation, and histopathology of lung cancer: a case-control study with the use of the Third National Cancer Survey. *J Natl Cancer Inst* 1983;70:421-426.
- Sundby P. Alcoholism and mortality. Universitets-forlaget, Oslo 1967.
- Teschke R, Neufeind M, Nishimura N, Strohmeyer G. Hepatic gamma-glutamyltransferase activity in alcoholic fatty liver: comparison with other liver enzymes in man and rats. *Gut* 1983;24:625-630.
- Thorarinsson AA. Mortality among men alcoholics in Iceland, 1951-74. *J Stud Alc* 1979;40:704-718.
- Tibblin G. A population study of 50-year-old men. An analysis of the non-participation group. *Acta Med Scand* 1965;178(4):453-459.
- Tibblin G. High blood pressure in men aged 50. A population study of men born in 1913. *Acta Med Scand* 1967; suppl. 470.
- Trell E, Dahlberg N, Larsson C, Krantz J-O, Lazer A, Petersson B-G. Interactive computer program for self-distributed medical questionnaire in a population health screening. *Computer Programs in Biomedicine* 1982;14:257-266.

- Trell E. Community-based preventive medical department for individual risk factor assessment and intervention in an urban population. *Prev Med* 1983; 12:397-402.
- Wilhelmsen L, Ljungberg S, Wedel H, Werkö L. A comparison between participants and non-participants in a primary preventive trial. *J Chron Dis* 1976;29: 331-339.
- Williams RR, Sorlie PD, Feinleib M, McNamara PM, Kannel WB, Dawber TR. Cancer incidence by levels of cholesterol. *JAMA* 1981;245:247-252.
- Wiseman SM, Spencer-Peet J. The effect of drinking patterns on enzyme screening tests for alcoholism. *Practitioner* 1977;219:243-245.
- Wu A, Slavin G, Levi AJ. Elevated serum gamma-glutamyl-transferase (transpeptidase) and histological liver damage in alcoholism. *Am J Gastroenterol* 1976; 65:318-323.
- Wälimäki M, Ylikahri R. Alcohol and sex hormones. *Scand J Clin Lab Invest* 1981;49:99-105.

Comparison of gamma-glutamyltransferase and other health screening tests in average middle-aged males, heavy drinkers and alcohol non-users

BO PETERSON, ERIK TRELL, HANS KRISTENSSON, GÖRAN FEX, MAURICE YETTRA* & BERTIL HOOD

Section of Preventive Medicine, Department of Internal Medicine, Department of Alcohol Diseases and Department of Clinical Chemistry, University of Lund, Malmö General Hospital, S-21401 Malmö, Sweden

Peterson, B., Trell, E., Kristensson, H., Fex, B., Yettra, M. & Hood, B. Comparison of gamma-glutamyltransferase and other health screening tests in average middle-aged males, heavy drinkers and alcohol non-users. *Scand. J. clin. Lab. Invest.* 43, 141–149, 1983.

Physical and biochemical health screening variables were compared in matched, middle-aged male samples of (a) ideological teetotallers, (b) average men, (c) self-reported alcohol abstainers, (d) low gamma-glutamyltransferase (GGT) activity, and (e–f) high GGT activity with or without admitted alcohol consumption background. The alcohol non-user groups and the individuals with low GGT had significantly lower mean values of relative body weight, pulse, systolic and diastolic blood pressure, haematocrit, serum urate, triglyceride, cholesterol, and zero and 120 min blood glucose than individuals with elevated GGT and alcohol overconsumption. The average men had intermediate levels. The frequency of increased values of the same tests was notably higher in the subjects with elevated GGT and heavy alcohol consumption than in the teetotallers and the other groups; and was lowest in the teetotallers.

Key-words: alcohol consumption; alcohol-related disabilities; gamma glutamyltransferase; health screening tests; prevention; teetotallers

Erik Trell, M.D., Department of Preventive Medicine, Malmö General Hospital, S-21401 Malmö, Sweden.

There have been many studies in recent years of gamma-glutamyltransferase (GGT) in indication of alcohol consumption and its complications, both in clinical materials of alcoholics

[30–32, 41] and in population investigations [1, 17, 24, 34–38]. No exact linear correlation between the absolute values of GGT and the momentary alcohol intake levels as expressed in drinks or grams of pure ethanol per day or week has been found [14, 17, 38]. However, the predominant background of elevated GGT in the majority of otherwise apparently healthy middle-aged males is offered by alcohol [17].

*Present address: Southern California Permanente Medical Group, Los Angeles, USA.

Consequently, GGT has been applied in conjunction with other analyses in indication, evaluation and prevention of drinking problems and disabilities [18].

The concept of alcohol-related disabilities has been introduced recently in order to distinguish and compare between the health hazards and health care implications of alcohol, and its consumption and dependency patterns [39]. The interrelations between these two aspects are not linear due to the individual differences in e.g. total exposure, metabolic handling and brand of alcohol and in susceptibility for and type of complication [8, 25]. However, elevated GGT has been shown to have a predominant alcohol background in about 75% of ordinary middle-aged men [17, 18]. It therefore would seem to represent an individual biological reaction useful in the early indication of alcohol-related disabilities.

We have previously reported associations between GGT, interview-assessed alcohol background and alcohol-related medico-social disturbances [17–19], retrospective and prospective morbidity [16, 19, 20], and prospective mortality [28] in the same population. GGT may also be utilized in the preventive programme as a biochemical feed-back and control instrument in further evaluation, treatment and control of drinking problems indicated by the test [18]. We here wish to report on the significant differences in several health screening analytes which we found in population subsamples with various levels of GGT and/or alcohol consumption.

MATERIAL AND METHODS

Study population

1. The screening population: All male residents of the city of Malmö with birth date in the years 1926–1929 were invited. The compliance rate was 75%. This group numbered 4763 men, all of whom were 48-years-old at the time of the screening.

2. GGT in top decile: a random half of all members in the 1926–1929 male birth-year cohorts with screening GGT in the top decile of the distribution were interviewed in detail as to their alcohol consumption habits. The methods and results of this investigation have been reported elsewhere [17]. The group finally consisted of 171 individuals, in 136 of whom a pre-

dominant alcohol background of the GGT elevation was confirmed; they were classified as heavy alcohol consumers, or alcohol-related (A) group, while 35 cases in whom no predominant alcohol background could be documented were classified as not alcohol-related (NA).

3. Low GGT group: A total subgroup of group 1, consisting of all individuals whose GGT levels were below the median of the screening distribution ($\leq 0.56 \mu\text{kat/l}$). This group numbered 2196 men.

Comparison groups

1. Teetotallers: As a comparison group we studied 52 middle-aged male members of the International Order of Good Templars (IOGT) in Southern Sweden (all who responded to the invitation). Not all of these were from the city of Malmö. The mean age was the same (48.8 years) as the other groups but with a larger range (38–55 years).

2. Abstainers: This group of alcohol non-users was established by 100 consecutive screening attenders born in 1927–1928 reporting 'yes' to the question 'Are you an alcohol abstainer?' in the screening questionnaire (this question was included from the 1927 birth year cohort). Subjects with psychiatric, anti-epileptic or anti-inflammatory drugs were excluded while a few individuals with known previous alcohol problems and recently or presently abstaining were included.

Screening investigation

All screening investigations were performed in the morning after an overnight fast. Venous blood samples were obtained in the supine position after a 10 min rest. Each individual answered an extensive questionnaire of about 260 questions. Social, psychological and medical history and health habits, such as tobacco and alcohol use, diet and physical activity were evaluated.

The height, weight, pulse and blood pressure at 0 and 10 min rest, triceps skinfold thickness, 12 lead electrocardiogram and pulmonary function tests were recorded. An extensive laboratory screening panel including a 2-h oral glucose tolerance test was done. All data were fed on-line into a computer and stored for later retrieval and study.

A relative weight index according to the formula: Actual (measured) weight/ideal weight

TABLE I. Mean values (m), standard deviations (SD) and reference values of actual/ideal weight (A/I W) (index), pulse at 0 min (P 0') (beats/min), recumbent systolic (BPS 10') and diastolic (BPD 10') blood pressures after 10 min rest (mmHg) and haematocrit (Hct) (%), in the study and comparison groups

	All males					GGT $\geq$ 1.44					GGT<0.54				
	NA		A			m		SD			m		SD		
	m	P ₂	m	m		m	SD	m	SD		m	SD	m	SD	
A/I W	1.09	0.14	<0.005	1.10	1.12	1.12	0.14	1.12	0.13		1.05	0.13	<0.0005	<0.0005	
P 0'	73	11	0.15	72	75	74	12	74	11		72	11	<0.0005	<0.0125	
BPS 10'	131	16	<0.0005	132	138	137	16	137	15		128	15	<0.0005	<0.0005	
BPD 10'	88	11	<0.0005	90	93	92	11	92	10		86	10	<0.0005	<0.0005	
Hct	43.8	2.7	<0.0005	43.6	44.9	44.6	2.6	44.6	2.5		43.5	2.5	<0.0005	<0.0005	

	IOGT teetotallers				Abstainers				Reference values	
	P ₁		P ₂		SD		P ₁		P ₂	
	m	SD	m	P ₂	m	SD	m	SD	m	P ₂
A/I W	1.08	0.14	—	<0.05	1.10	0.17	—	0.15	0.9–1.2	
P 0'	71	9.4	—	0.05	74	12	—	—	55–85	
BPS 10'	128	12.5	<0.05	<0.0005	128	16	<0.05	<0.0005	≤150	
BPD 10'	88	9.7	—	0.01	90	10	<0.05	<0.1	≤95	
Hct	42.9	2.3	<0.01	<0.0005	43.4	2.8	<0.1	<0.0005	39–49	

P₁ = significant levels of differences in relation to the whole sample of middle-aged males, P₂ = significant levels of differences in relation to the whole group of screening GGT $\geq$ 1.44 μ kat/l. A = alcohol-related, NA = non-alcohol-related subgroups of GGT in top decile.

TABLE II. Fasting blood glucose (G 0') and blood glucose at 120 min (G 120') in oral glucose tolerance test (mmol/l), serum urate ($\mu\text{mol/l}$), calcium (mmol/l), creatinine ($\mu\text{mol/l}$), triglycerides, cholesterol (both mmol/l) and gamma-glutamyltransferase ($\mu\text{kat/l}$) in the same groups

	All males				GGT ≥ 1.44				GGT < 0.54			
	NA		A									
	m	SD	P_2	m	m	SD	m	SD	m	SD	P_1	P_2
G 0'	4.62	0.8	<0.0005	4.79	5.02	0.9	4.96	0.9	4.54	0.65	<0.0005	<0.0005
G 120'	5.43	1.62	<0.0005	5.89	5.97	1.8	5.95	1.8	5.16	1.14	<0.0005	<0.0005
Urate	307	62	<0.0005	338	351	77	348	77	296	59	<0.0005	<0.0005
Ca	2.42	0.08	<0.0005	2.44	2.46	0.09	2.45	0.09	2.42	0.08	—	<0.0005
Creat	94.7	12.7	<0.0025	94.9	90.7	13.4	91.6	13.4	95.1	12.7	0.1	<0.0005
Tg	1.56	0.89	<0.0005	2.04	2.45	1.3	2.37	1.3	1.53	0.54	<0.1	<0.0005
Chol	5.81	1.05	<0.0005	6.04	6.15	1.17	6.12	1.17	5.64	0.96	<0.0005	<0.0005
GGT	0.83	0.95	()	2.60	3.04	1.9	2.95	1.9	()	()	()	()

	IOGT teetotallers				Abstainers				Reference values	
	P_1		P_2		P_1		P_2			
	m	SD	P_1	P_2	m	SD	P_1	P_2		
G 0'	4.69	1.25	—	<0.05	4.56	0.79	—	<0.0005	3.3–5.5	
G 120'	5.32	1.45	—	<0.01	5.57	1.61	—	<0.05	≤7.0	
Urate	294	59	—	<0.0005	284	67	<0.0005	<0.0005	180–480	
Ca	2.42	0.09	—	<0.025	2.40	0.1	<0.01	<0.0005	2.2–2.6	
Creat	101	14.4	<0.0025	<0.0005	96.1	12.9	—	<0.005	80–115	
Tg	1.45	0.43	—	<0.0005	1.51	0.84	—	<0.0005	≤2.2	
Chol	5.43	1.02	<0.005	<0.0005	5.53	0.94	0.005	<0.0005	≤7.7	
GGT	0.58	0.40	<0.05	()	0.72	0.49	0.1	()	≤1.08	

P_1 and P_2 are explained in the legend to Table I.

for sex, age and body height (A/I weight) was calculated by the computer for each individual. The tables of Lindeberg *et al.* [22] were used as ideal weight reference.

GGT was analysed by standard methods at the Department of Clinical Chemistry, Malmö General Hospital [6]. Serum concentrations of sodium, potassium and calcium were determined by flame photometry. Triglyceride, cholesterol, urate and glucose were determined enzymatically. Albumin was determined with a dye-binding method (bromocresol-green) and creatinine with Jaffe's alkaline picrate method. The laboratory values are here expressed in SI units. Reference ranges at our laboratory are given in Tables I-II.

Statistical methods

The significance levels of differences in mean values between groups were calculated by Student's *t*-test and in frequencies by the χ^2 -test. P_1 expresses the significance level in relation to the whole screening population (study group 1) and P_2 in relation to the alcohol-related GGT elevation group (study group 2).

RESULTS

Figure 1 shows that the distribution of GGT in the whole screening population is skewed to the right in comparison with the IOGT group of ideological teetotallers.

In Tables I-II, mean values and standard deviations of several screening tests are compared in the groups. Included are the *P* values of significant differences in relation to group 1 (P_1)

and group 2 (P_2). Significant differences between the whole study population and the IOGT members were present for recumbent blood pressure after 10 min rest, haematocrit, serum albumin, serum creatinine, cholesterol and GGT. The differences of all these tests except albumin between the teetotallers and the group of elevated GGT were even more significant, and in addition there were significant differences between A/I weight, pulse, recumbent diastolic blood pressure after 10 min rest, serum urate, fasting blood glucose and serum triglycerides. Also in relation to the whole group of middle-aged men the differences were present, although with less pronounced statistical significance. In the cases of GGT elevation with confirmed alcohol background (A) the differences tended to be even higher than in the whole group of increased GGT. The tests which did not show equally significant differences between the groups include (triceps) skinfold thickness, pulse after 10 min rest, serum sodium, potassium and calcium (not shown).

In general the self-reported abstainers and the group of GGT values below the median had very similar values as the IOGT members (Tables I-II). In Fig. 2, the distribution of the systolic blood pressure values after 10 min rest in the latter subjects is compared with the alcohol-related GGT elevation group. It is seen that even small differences of mean values between the groups may be associated with a more pronounced redistribution of the test results, with an increased frequency of abnormality high values. In Fig. 3, the prevalence of borderline high screening levels of relative body weight, pulse at 10 min, recumbent diastolic blood pressure at 10

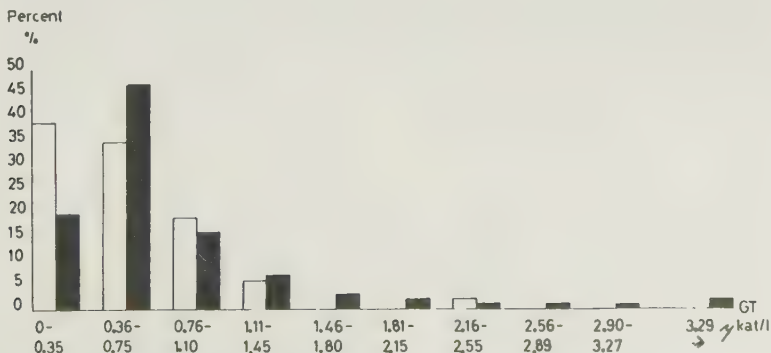


FIG. 1. Screening GGT distribution in teetotallers (white columns) and the total screening cohort of males in the same age (men born 1926-1929, black columns).

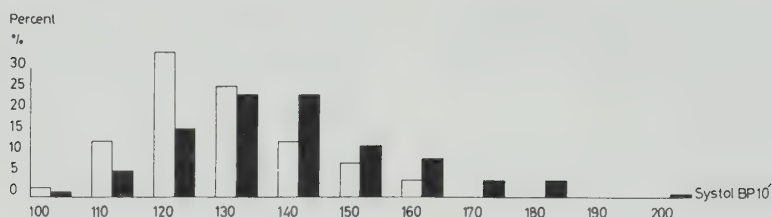


FIG. 2. Distribution of recumbent systolic blood pressure at 10 min in teetotallers (white columns) and heavy alcohol consumers (black columns) (The A (alcohol-related) subgroup of GGT in top decile).

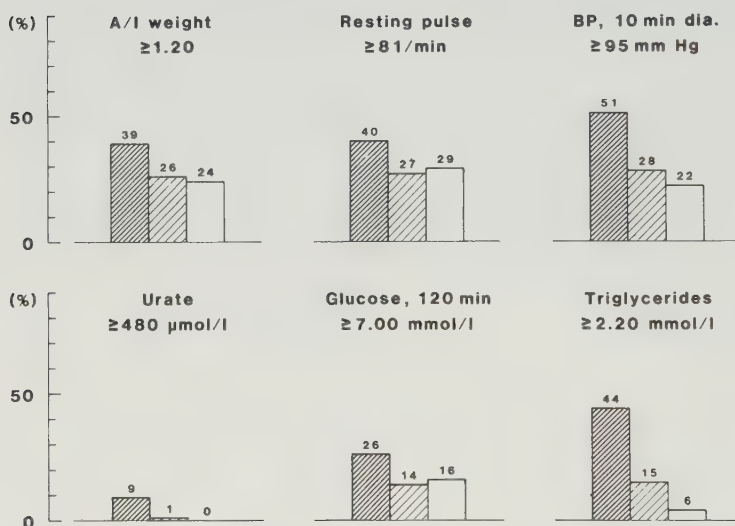


FIG. 3. Frequency of borderline high screening values of relative body weight, pulse at 0 min, recumbent diastolic blood pressure at 10 min, serum urate, blood glucose at 120 min in oral glucose tolerance tests, and serum triglycerides in the heavy drinkers (group 2A, filled columns), the whole screening cohort (group 1, half-tone columns) and teetotallers (IOGT, white columns). The statistical significance of the differences between heavy drinkers and the whole cohort (a) and the teetotallers (b) were: Body weight; <0.001 (a) and <0.05 (b), pulse 0 min; <0.005 (a) and $0.10-0.20$ (b), recumbent diastolic blood pressure at 10 min; <0.0005 (a) and <0.025 (b), 120' blood glucose; <0.0005 (a) and $0.10-0.20$ (b), and serum triglycerides; <0.0005 (a and b). (■) Heavy drinkers ($n = 136$), (▨) whole cohort ($n = 4763$), (□) teetotallers ($n = 51$).

min, serum urate, blood glucose at 120 min in oral glucose tolerance tests, and serum triglycerides are compared in the same two groups and the whole screening cohort. In the alcohol-related GGT elevation group a significantly higher frequency of values which exceed our cut-off levels for further investigation and treatment is apparent.

DISCUSSION

Elevated values of GGT represent a biological reaction which in the majority of otherwise healthy middle-aged men has a predominant alcohol background [17]. It would thus seem possible to apply GGT in the field of alcohol-related disabilities and their early recognition, control and

prevention in individuals. We have studied GGT both retrospectively and prospectively according to these principles and have found associations between GGT and sickness days, alcohol-related morbidity and mortality [16, 19, 20, 28] which indicate that GGT may identify individuals with actual problems or presently at risk because of their alcohol exposition. We have also found associations between GGT, alcohol background and many of the biometrical screening tests which we consider to be of importance in the assessment and management of the overall health status in our preventive medical programme.

Significant covariations existed already in the low and normal ranges of the distribution of several different tests, but there was also an increased frequency of borderline high values in the cases with elevated GGT, particularly those with alcohol background (Fig. 3). It is interesting that although these data were obtained in attenders to a voluntary health screening investigation and thus mainly correspond to the normal test variability range in presymptomatic individuals, they parallel previous reports of overt disease complications in chronic alcoholism. From such materials, adverse effects of alcohol upon uric acid and lipid metabolism are well known [1, 3, 4, 9, 21, 26, 27, 36, 37], and there are also reports of negative influences of alcohol on glucose tolerance [11, 23, 26, 29], blood pressure [2, 7, 10, 12, 13, 15, 25, 26] and haematological variables [1, 33, 40]. Also low creatinine has been observed in alcoholism [5], but the mechanism of this finding, which was present also in our study, is not clear.

In severe acute alcoholism and in the late stages of alcoholic liver disease, serum electrolyte disturbances, hypocalcaemia, hypoalbuminaemia etc. are well-known occurrences but these were not seen in our material. We originally thought that the individuals in group 2 with very high GGT levels (arbitrarily chosen at $4.32 \mu\text{kat/l}$, which deleted the 25 highest values) should be excluded from the material because it was suspected that they might have overt alcoholic liver disease. However, when we compared these 25 cases with the remaining group (not shown), all the mean values were the same, except, of course, GGT.

The different groups in the present study all represent consecutive total subsamples of a pre-clinical, apparently healthy screening popula-

tion. It is noteworthy that although significant differences existed in many of the variables between the groups, all the mean values (except the diastolic blood pressure at 10 min and the serum triglycerides in the high alcohol consumption group) were still within the normal range. In spite of the high *P*-values the absolute differences were thus in general rather unimpressive; and the high *P*-values mainly caused by the large number of subjects. The practical significance of the differences may therefore sometimes be questionable. Nonetheless, the added implication of several variables in the upper normal range in an individual's screening profile would still seem to represent an impaired health status [34]. Furthermore, as exemplified by the tests in Fig. 3, a higher normal mean value of some variable in the heavy alcohol consumers was associated with a significantly higher frequency of individuals in this group with a borderline or pathological level of that test than in teetotallers and the whole screening cohort.

However, most test values in healthy middle-aged males naturally lie between the normal limits and it is interesting that GGT and broad alcohol consumption categories showed significant associations with many important health screening variables also within their ordinary range. This indicates both that GGT is more powerful than the others as an independent screening instrument for alcohol-related disturbances and that GGT and assessment of alcohol background are relevant also in the investigation and care of the premorbid somatic health in middle-aged males.

ACKNOWLEDGMENTS

This study was supported by grants from the Swedish Council for Planning and Coordination of Research (B.P.) and the Swedish Delegation for Social Research, Ministry of Health and Social Affairs (H.K.).

REFERENCES

- 1 Bagrel, A., d'Houtaud, A., Gueguen, R. & Siest, G. Relation between reported alcohol consumption and certain variables in an unselected population. *Clin. Chem.* **25**, 1242, 1979.
- 2 Beevers, D.G. Alcohol and hypertension. *Lancet* **ii**, 114, 1977.

- 3 Castelli, W.P., Gordon, T., Hjortland, M.C., Kagan, A., Doyle, J.T. & Hames, C.G. Alcohol and blood lipids. The co-operative lipoprotein study. *Lancet* **ii**, 319, 1962.
- 4 Chait, A., Mancini, M., February, A.W. & Lewis, B. Clinical and metabolic study of alcoholic hyperlipidemia. *Lancet* **ii**, 62, 1972.
- 5 Chan-Yeng, M., Ferreira, P., Frolich, J. & Tan, F. The effects of age, smoking and alcohol on routine laboratory tests. *Am. J. clin. Path.* **75**, 320, 1981.
- 6 Committee on enzymes of the Scandinavian Society for Chemistry and Clinical Physiology. Recommended methods for the determination of gamma-glutamyl transferase in blood. *Scand. J. clin. Lab. Invest.* **36**, 119, 1976.
- 7 D'Alonzo, C.A. & Pell, S. Cardiovascular disease among problem drinkers. *Occup. Med.* **10**, 344, 1968.
- 8 Fraser, G.E. & Upsdell, M.B. Alcohol and other discriminants between cases of sudden death and myocardial infarction. *Amer. J. Epidemiol.* **114**, 462, 1981.
- 9 Ginsburg, H., Olefsky, J., Farquhar, J.W. & Reaven, G.M. Moderate ethanol ingestion and plasma triglyceride levels. *Ann. Intern. Med.* **80**, 143, 1974.
- 10 Gyntelberg, F. & Meyer, J. Relationship between blood pressure and physical fitness, smoking and alcohol consumption in Copenhagen males aged 40-59. *Acta. Med. Scand.* **195**, 375, 1974.
- 11 Hed, R. Clinical studies in chronic alcoholism II. Carbohydrate metabolism in chronic alcoholism with particular reference to glucose and insulin tolerances. *Acta Med. Scand.* **162**, 195, 1958.
- 12 Henningsen, N.C., Ohlsson, O., Mattiasson, I., Trell, E., Kristensson, H. & Hood, B. Hypertension, levels of serum gamma glutamyl transpeptidase and degree of blood pressure control in middle-aged males. *Acta Med. Scand.* **207**, 245, 1980.
- 13 Henningsen, N.C., Hood, B., Mattiasson, I., Trell, E. & Kristensson, H. Alcohol and hypertension. *Lancet* **ii**, 121, 1981.
- 14 Hood, B. Tracing and handling of high alcohol consumption with the aid of laboratory means. *Eur. J. clin. Invest.* **11**, 147, 1981.
- 15 Klatsky, A.L., Friedman, G.D., Siegelaub, A.S., & Gérard, M.J. Alcohol consumption and blood pressure. Kaiser Permanent Multiphasic Health Examination data. *N. Engl. J. Med.* **296**, 1194, 1977.
- 16 Kristensson, H., Peterson, B., Trell, E. & Hood, B. Hospitalization and alcohol-related morbidity within three years after screening in middle-aged men. *Drug Alc. Dep.* **9**, 325, 1982.
- 17 Kristensson, H., Trell, E., Fex, G. & Hood, B. Serum gammaglutamyltransferase. Statistical distribution in a middle-aged male population and evaluation of alcohol habits in individuals with elevated levels. *Prev. Med.* **9**, 108, 1980.
- 18 Kristensson, H., Trell, E. & Hood, B. Serum- γ -glutamyltransferase in screening and continuous control of heavy drinking in middle-aged men. *Amer. J. Epidemiol.* **114**, 862, 1981.
- 19 Kristensson, H., Öhrn, J. & Hood, B. Convictions for drunkenness or drunken driving, sick absenteeism and morbidity in middle-aged males with different levels of serum- γ -glutamyl-transferase. *Prev. Med.* **11**, 403, 1982.
- 20 Kristensson, H., Öhrn, J., Trell, E. & Hood, B. Serum gamma-glutamyl-transferase at screening and retrospective sickness days. *Lancet* **i**, 1141, 1980.
- 21 Lieber, C.S. & Davidson, C.S. Some metabolic effects of ethyl alcohol. *Am. J. Med.* **33**, 319, 1962.
- 22 Lindeberg, W., Natvig, H., Rygh, A. & Svendsen, K. Høyde og vektundersøkelser hos voksne menn og kvinner. *Tidsskr. Norsk Laegeforen.* **76**, 361, 1956.
- 23 Lundquist, G. Glucose tolerance in alcoholism. *Br. J. Addict.* **61**, 51, 1965.
- 24 Martin-Boycie, A., Schwartz, D., Dreyfus, & Schneegans, P. Biochemical and haematological markers of alcohol intake. *Lancet* **i**, 978, 1978.
- 25 Mitchell, P.J., Morgan, M.J. & Boaddle, D.J. Role of alcohol in the aetiology of hypertension. *Med. J. Aust.* **ii**, 198, 1980.
- 26 Myrhed, M. Alcohol consumption in relation to factors associated with ischemic heart disease. *Acta. Med. Scand. Suppl.* **567**, 1974.
- 27 Ostrander, L.D., Lamphiear, D.E., Block, W.D., Johnson, B.C., Ravenscroft, C. & Epstein F.H. Relationship of serum lipid concentrations to alcohol consumption. *Arch. Intern. Med.* **134**, 451, 1974.
- 28 Peterson, B., Kristensson, H., Sternby, N.H., Trell, E., Fex, G. & Hood, B. Alcohol consumption and premature death in middle-aged men. *Br. Med. J.* **280**, 1403, 1980.
- 29 Rehfeld, J.F., Juhl, E. & Hilden, M. Carbohydrate metabolism in alcohol-induced fatty liver. *Gastroenterology* **64**, 445, 1973.
- 30 Rollason, J.G., Pincherle, G. & Robinson, D. Serum gamma-glutamyl transpeptidase in relation to alcohol consumption. *Clin. chim. Acta* **39**, 175, 1972.
- 31 Rosalki, S.B. Screening test for alcoholism. *Lancet* **ii**, 843, 1973.
- 32 Rosalki, S.B. & Rau, D. Serum gamma-glutamyl transpeptidase activity in alcoholism. *Clin. chim. Acta* **39**, 41, 1972.
- 33 Smith, J.F.B. & Lucia, N.P. Alcohol—a cause of stress erythrocytosis? *Lancet* **i**, 637, 1973.
- 34 Trell, E., Peterson, B., Kristensson, H., Fex, G., Larne, P., Yettra, M. & Hood, B. Serum gamma-glutamyl transferase and a somatic health score in middle-aged men. *Ann. clin. Biochem.* **17**, 143, 1980.
- 35 Waern, U., Boberg, J. & Hellsing, K. Evaluation of indices of alcohol intake in a population of 60-year-old men in Uppsala, Sweden. *Acta. Med. Scand.* **205**, 353, 1979.
- 36 Whitehead, T.P., Clarke, C.A. & Whitfield, A.G.W. Biochemical and haematological markers of alcohol intake. *Lancet* **i**, 978, 1978.
- 37 Whitfield, J.B., Hensley, W.J., Bryden, D. & Gallagher, H. Some laboratory correlates of drinking habits. *Ann. clin. Biochem.* **15**, 297, 1978.

- 38 Whitfield, J.B., Hensley, W.J., Bryden, D. & Gallagher, H. Estimation of alcohol intake from laboratory results. *Ann. clin. Biochem.* **15**, 304, 1978.
- 39 WHO. Alcohol-related disabilities. *WHO Offset. Publ.* **32**, 1, 1977.
- 40 Wu, A., Chavarin, I. & Levi, A.J. Macrocytosis of chronic alcoholism. *Lancet* **i**, 829, 1974.
- 41 Wu, M.B., Slavin, G. & Levi, A.J. elevated serum gamma-glutamyl transferase and histological liver damage in alcoholism. *Am. J. Gastroenterol.* **65**, 318, 1976.

Received 29 April 1982

Accepted 25 November 1982

Serum gamma-glutamyl transferase and a somatic health score in middle-aged men

E TRELL, B PETERSSON, H KRISTENSON, G FEX, P LARME, M YETTRA,* AND B HOOD

From the Section of Preventive Medicine, Department of Alcohol Diseases, Department of Internal Medicine, and Department of Clinical Chemistry, University of Lund, Malmö General Hospital, S-214 01 Malmö, Sweden

SUMMARY In an ongoing population investigation of middle-aged men in Malmö, Sweden, several health screening variables showed strong but crude individual covariations with the level of the hepatic enzyme, serum gamma-glutamyl transferase (GGT). These variables were combined, according to an analysis of their normal distributions, into a score index which exhibited a much smoother correlation with low, normal, and elevated levels of GGT when tested in a random population subsample. It is concluded that this scoring system may find further utilisation as a general descriptive method of recording statistical covariations between health screening tests and sum them up.

Serum gamma-glutamyl transferase (GGT) is a sensitive marker of alcohol effects on the liver, increased values representing either parenchymatous liver damage, enzyme induction, or other metabolic mechanisms.¹ The relation between GGT and alcohol consumption has been documented mostly in clinical studies of alcoholics,^{2–4} but also in a number of population investigations elevated GGT levels were found to correlate with increased alcoholic intake.^{5–12} Covariations between alcohol intake and body weight,^{13–14} blood pressure,^{13–15–18} pulse,^{15–16} blood lipids,^{16–19–22} serum urate,^{6–7–9–16–23} impaired glucose tolerance,^{16–24–28} and elevations of various hepatic enzymes such as ALAT and ASAT²⁹ have been reported as well.

Factors that influence GGT levels in population screening investigations would thus appear to be associated also with changes in a number of other health tests. In an ongoing screening programme in Malmö, we therefore evaluated correlations between GGT levels and other variables measured in a multiphasic health investigation in a middle-aged male population.^{11–12}

We here describe the construction of a scoring system which is representative of a summation of several of these variables in each individual.

Material and methods

SCREENING INVESTIGATIONS

All male Malmö residents born in 1926, 1927, 1928,

* Present address: Southern California Permanente Medical Group, Los Angeles, USA.

1929, and 1930 were invited to the Department of Preventive Medicine, Malmö General Hospital, between the years 1974 and 1978. The participation rate after two invitations in these five birth-year cohorts was around 75%.

All screening investigations were performed in the morning after an overnight fast. Venous blood samples were obtained in the supine position after 10 minutes' rest.

Weight and height were measured by routine technique. A relative weight index according to the formula: Actual (measured) weight/Ideal weight for body height (A/I-weight) was calculated for each individual. The tables of Lindeberg *et al*³⁰ were used as ideal weight reference.

Pulse and systolic and diastolic blood pressure were also measured by standard methods at 0 and 10 minutes rest, in both the standing and recumbent positions.

In the oral glucose tolerance test, 30 g glucose/m² body surface area as a 10% aqueous solution was ingested within 5 minutes, and (fingertip capillary) blood glucose was determined at 0, 5, 20, 30, 40, 50, 60, 70, 90, and 120 minutes (in duplicate at 0 and 120 minutes).

GGT was determined according to the suggestions of the Scandinavian Enzyme Committee at the Department of Clinical Chemistry, Malmö General Hospital.³¹ All the other laboratory tests referred to here were also performed according to standard techniques at the Department of Clinical Chemistry, Malmö General Hospital. Their values are here

expressed in SI units. Their upper normal reference values in middle-aged men in Malmö are shown in Table 1, and their distributions are represented by the quintile limit values in Table 2 and Figs 1–3.

STATISTICAL METHODS

The quintile distributions of all variables utilised in

the score were determined in the total screening cohort of males born in the years 1926–29 (screening participants, $n = 4700$) and were used as 'reference quintiles' in obtaining comparisons of variables between GGT-low and GGT-high population subsamples,^{11,12} and also in calculating individual quintile scores as described in detail below.

Results

In Figs 1 and 2 we show the distribution of pulse after 10 minutes' rest, recumbent systolic blood pressure at 10 minutes, recumbent diastolic blood pressure at 10 minutes, A/I-weight, blood glucose and serum insulin at 120 minutes in oral glucose tolerance tests, serum triglycerides, urate, asparagine-aminotransferase (ASAT) and alanine-aminotransferase (ALAT) in the whole population as compared with two polar subgroups consisting of the individuals with low GGT and with high GGT and admitted high alcohol consumption.¹² The distribution of the aforementioned variables in the whole population was divided into quintiles, each consisting of as close to 20% of the population as possible. Above each quintile column in the figures is indicated the upper limit for this quintile of each of the tests. This provides a reference against which the distribution of the same variables in the GGT-low and GGT-high population subsamples could be compared. In each of the tests one can see divergence of the distributions with a smaller percentage of the

Table 1 Units and upper normal values of pulse at 10 minutes, recumbent systolic blood pressure at 10 minutes, recumbent diastolic blood pressure at 10 minutes, actual/ideal weight, blood glucose and serum insulin at 120 minutes in oral glucose tolerance tests, serum triglycerides, urate, asparagine aminotransferase (ASAT), alanine-aminotransferase (ALAT), phosphate, haematocrit, skinfold index, serum cholesterol, and γ -glutamyl transferase (GGT) in middle-aged men in Malmö.

Variable	Unit	Upper normal range limit
Pulse 10 min	beats/min	90
BP systol 10 min	mm Hg	150
BP diastol 10 min	mm Hg	95
A/I weight	index	1.10
Glucose 120 min	mmol/l	7.0
Insulin 120 min	mIU/l	60
Triglycerides	mmol/l	2.2
Urate	μ mol/l	480
ASAT	μ kat/l	0.67
ALAT	μ kat/l	0.67
Skinfold	log scale	—
Cholesterol	mmol/l	7.7
Phosphates	mmol/l	1.3
Haematocrit	per cent	49
GGT	μ kat/l	1.08

A/I = actual/ideal

Table 2 Calculation of quintile score in a (fictitious) member of the 1930 birth-year cohort

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Score value	0	2	4	6	8
Pulse 10 min	≤ 60	61–67	68–70	71–77	≥ 78
68			4		
BP systol 10 min	≤ 115	120–125	130	135–140	≥ 145
125		2			
BP diastol 10 min	≤ 75	80–85	90	95	≥ 100
75					
A/I weight	≤ 0.99	1.0–1.05	1.06–1.13	1.14–1.21	≥ 1.22
1.31					8
Glucose 120 min	≤ 4.02	4.03–4.83	4.84–5.64	5.65–6.65	≥ 6.66
6.8					8
Insulin 120 min	≤ 13	13.1–21.0	21.1–33.4	33.5–55.6	≥ 55.7
80					8
Triglycerides	≤ 1.00	1.01–1.27	1.28–1.52	1.53–2.03	≥ 2.04
3.25					8
Urate	≤ 257	258–292	293–323	324–358	≥ 359
340				6	
ASAT	≤ 0.31	0.32–0.36	0.37–0.41	0.42–0.49	≥ 0.50
0.48				6	
ALAT	≤ 0.26	0.27	0.35–0.41	0.42–0.56	≥ 0.57
0.38			4		
Total	0	2	8	12	32 54

As shown under the designations of the respective variables in the table, this man had pulse at 10 min 68 beats/min; recumbent systolic blood pressure at 10 min 125 mm Hg; recumbent diastolic blood pressure at 10 min 75 mm Hg; actual/ideal weight 1.31; blood glucose at 120 min in oral glucose tolerance test 6.8 mmol/l; serum insulin at 120 min in oral glucose tolerance test 80 mIU/l; serum triglycerides 3.25 mmol/l; serum urate 340 μ mol/l; ASAT 0.48 μ kat/l; and ALAT 0.38 μ kat/l. These values were allocated to the corresponding quintile columns, yielding their respective score numbers (0 for the first quintile, 2 for the second quintile, 4 for the third quintile, 6 for the fourth quintile, and 8 for the fifth quintile). Adding up the score numbers of the 10 variables gave a total score value of 54 in this example.

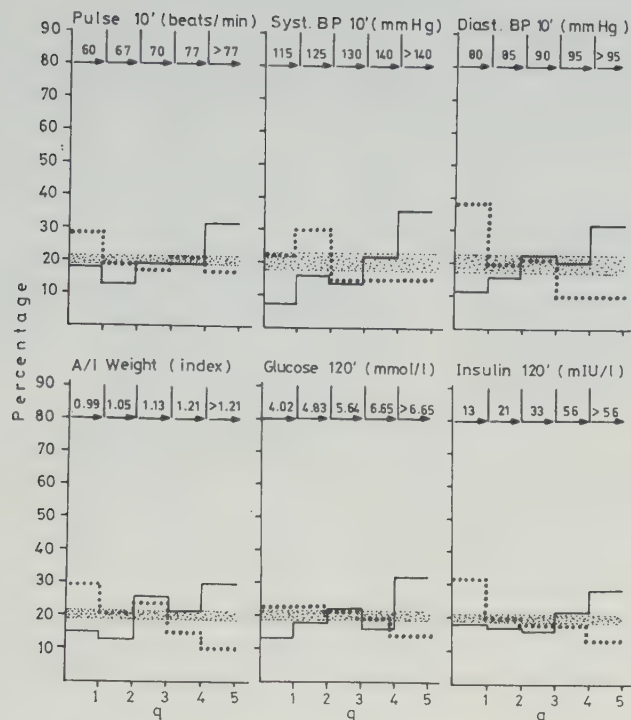


Fig. 1 Relative distributions of pulse after 10 minutes' rest, recumbent systolic blood pressure at 10 minutes, recumbent diastolic blood pressure at 10 minutes, actual/ideal weight and blood glucose and insulin at 120 minutes in oral glucose tolerance tests in the whole screening cohort (half-tone horizontal band) as compared with two polar subgroups consisting of the subjects with low GGT (GGT left to the median, $\leq 0.54 \mu\text{kat/l}$, dotted line; $n = 2190$) and with high GGT and admitted high alcohol consumption ($\geq 1.44 \mu\text{kat/l}$, solid line; $n = 136$). The half-tone horizontal band at the 20% level shows that the distribution of these test variables in the whole screening cohort was divided into quintiles, each consisting of as close to 20% of the cohort as possible (in a few of the variables, eg, blood pressure which was measured to 5 mm Hg, there was not exactly 20% of the total screening cohort in each column; this is indicated by the broadness of the band). Above each quintile column is indicated the upper limit for this quintile of each test value. This provides a reference against which the percentage distribution of the same test values in the GGT-low and GGT-high population subsample could be compared. q = quintile.

high GGT group in the lower reference quintiles and a larger percentage in the high quintiles (and the opposite in the low GGT group).

This supports individual but rather crude associations between all of these test factors and GGT. We investigated several other screening variables in this way, eg, phosphate, haematocrit, skinfold index, and serum cholesterol, but found the associations were weaker (Fig. 3). Therefore we decided to use the 10 tests shown in Figs 1 and 2 for the construction of a test score.

In 574 consecutive randomly selected males born in 1930 (half of the participants of this birth-year cohort) we added the quintile score value of each of the 10 tests (Table 2). We arbitrarily assigned the score value of 0 to the lowest quintile, and two additional points for each higher quintile, so that the highest quintile score of each variable was 8. Theoretically, the lowest possible total score of the 10 variables would be 0, and the highest 80.

As shown in Fig. 4, the actual score values in the 574 males ranged between 2 and 80, with an apparently normal distribution. The relationship between the score values and the GGT levels in the

574 males is summarised in Table 3. In our opinion, the Table shows that the addition into a combined index of the 10 variables, each of which exhibited a crude association with GGT only in polar subgroups

Table 3 (A) Mean values ($\bar{m}$) and standard deviation (SD) of GGT in increasing levels (as close to deciles as possible) of score results in random half of 1930 birth-year cohort

(B) Approximate mean values and standard deviation of score results in increasing levels of GGT (as close to deciles as possible) in random half of 1930 birth-year cohort

(A)				(B)			
Score	n	GGT		GGT	n	Score	
		$\bar{m}$	SD			$\bar{m}$	SD
2-18	53	0.40	0.13	0.22-0.31	57	27	12
20-22	42	0.43	0.13	0.32-0.35	53	30	11
24-26	51	0.49	0.29	0.36-0.38	46	31	12
28-30	66	0.52	0.23	0.39-0.44	73	34	14
32-34	62	0.56	0.34	0.45-0.49	58	37	14
36-38	46	0.65	0.56	0.50-0.56	53	36	6
40-44	67	0.72	0.77	0.57-0.67	56	38	13
46-50	66	0.81	0.61	0.68-0.81	56	43	14
52-58	66	1.08	0.94	0.82-1.33	64	46	13
60-80	53	1.39	1.60	1.34-14.40	57	54	12

of the screening cohort, resulted in a much smoother correlation over the whole range of GGT in the total population subsample so analysed. The correlation is even better in the low range of GGT (and score results) than in the higher levels.

Discussion

There are earlier reports of correlations between GGT and body weight,³² blood pressure and pulse,¹¹ serum triglycerides,³³ serum urate,⁹ glucose tolerance,¹¹ and ALAT and ASAT.^{9,29} All these correlations are most evident in polar, GGT-low, and GGT-high subgroups, which, however, are quantitatively small in the population.^{11,12} Further, even in these subgroups the correlation of each of the variables alone with GGT is rather crude (Figs 1 and 2). The

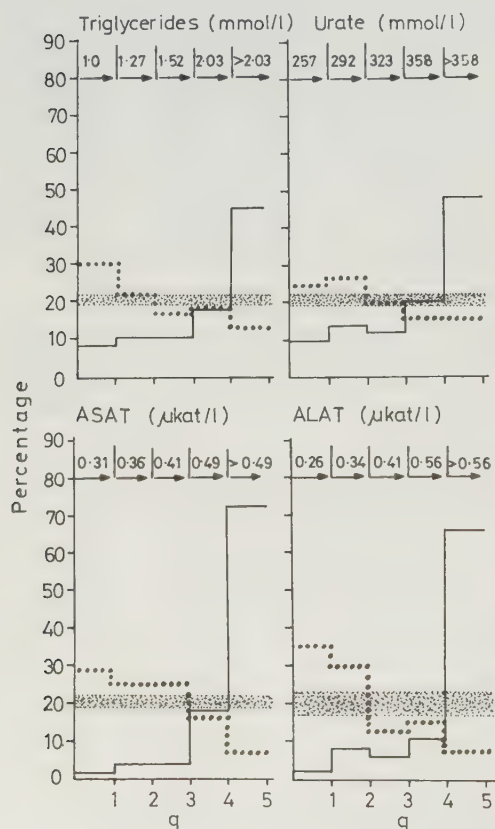


Fig. 2 Relative distributions of serum triglycerides, urate, asparagine-aminotransferases (ASAT), and alanine-aminotransferase (ALAT) in the same groups as in Fig. 1.

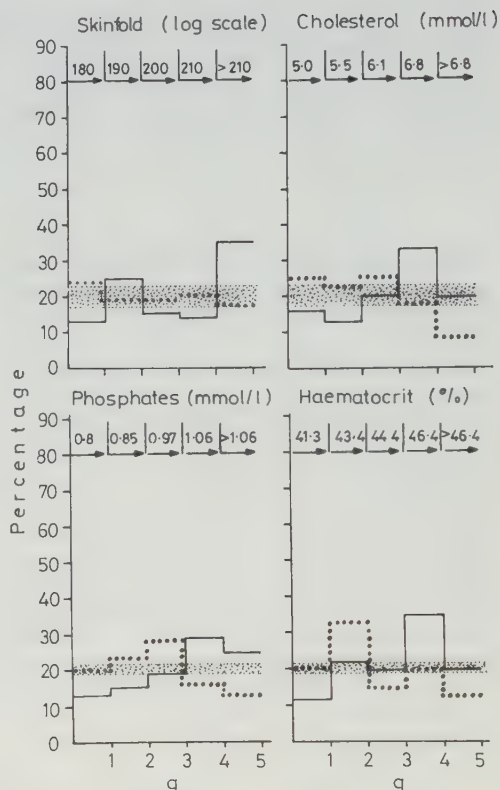


Fig. 3 Relative distributions of skinfold index, serum cholesterol, phosphates, and haematocrit in the same groups as in Figs 1 and 2.

score, which we constructed on the basis of an analysis of several variables relating to the GGT level, seems to exhibit a smooth correlation with GGT over the whole normal range (Table 3). The correlation in the low GGT range is, in our opinion, as good as in the abnormal GGT range. Since the score is derived from tests relevant to the general health of the individual, one suspects that the association of low GGT levels and low score values may be as predictive of good health as high score values are of impaired health.

The other starting points for our scoring system were the reported effects of alcohol on a variety of health screening tests and the evidence that GGT may offer a sensitive biochemical correlate to alcohol consumption levels in the population. There are earlier scores relating to alcohol consumption.³⁴ However, these are derived from clinical symptoms

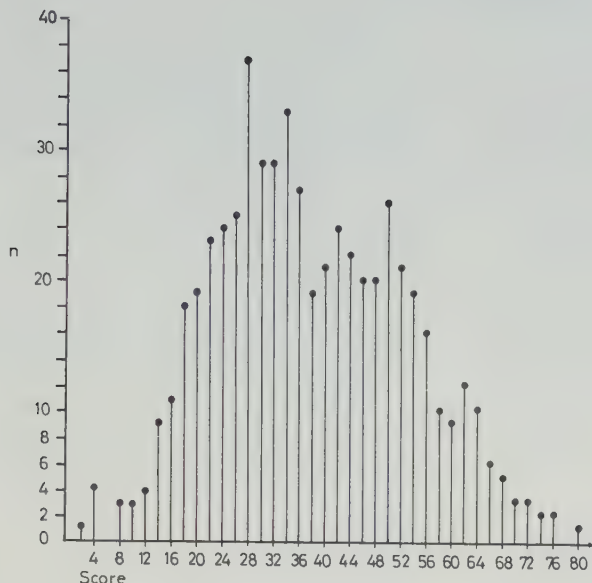


Fig. 4 Distribution of score values in random half of 1930 birth-year cohort; n = number of individuals.

of overt alcoholism, and biochemical indications of alcohol consumption utilising not only single analyses such as GGT but a combined index of test variables influenced by alcohol have been requested.⁸ We therefore thought it relevant to base the descriptive formulation and evaluation of the scoring system on comparisons with GGT. However, it is obvious that this methodological approach will bias the cause-and-effect interpretation of the score, in regard both to GGT and to the interrelations between the individual tests of which the score is composed. It is also important to emphasise that it is impossible to draw any conclusions as to the actual correlation of the score results with alcohol consumption levels until the appropriate investigations of this have been performed. Such studies are under way, in which also the possibility of utilising modified versions of the score by exclusion of some of its test components and/or inclusion of additional physical, biochemical, and anamnestic data relating to alcohol consumption^{8,9} will be investigated. Furthermore, since the score represents a general descriptive method of recording statistical covariations between health screening tests and sums them up, it should be possible to utilise the same scoring principle in other fields of study, for instance, cardiovascular morbidity and mortality.

This study was supported by groups from the Swedish Delegation for Social Research, Ministry of Health

and Social Affairs (UK), and the Swedish Council for Planning and Coordination of Research (BP).

References

- ¹ Rosalki S B. Serum gamma-glutamyl transpeptidase. *Adv Clin Chem* 1975; **17**: 53–103.
- ² Rollason J G, Pincherle G, Robinson D. Serum gamma-glutamyl transpeptidase in relation to alcohol consumption. *Clin Chim Acta* 1972; **39**: 75–80.
- ³ Rosalki S B, Rau D. Serum gamma-glutamyl transpeptidase activity in alcoholism. *Clin Chim Acta* 1972; **39**: 41–47.
- ⁴ Wu M B, Slavin G, Levi A J. Elevated serum gamma-glutamyl transferase and histological liver damage in alcoholism. *Am J Gastroenterol* 1976; **65**: 318–323.
- ⁵ Martin-Boyer A, Schwartz D, Dreyfus J, Schneegans P. Biochemical and haematological markers of alcohol intake. *Lancet*, 1978; **2**: 529.
- ⁶ Whitehead T P, Clarke C A, Whitfield A G W. Biochemical and haematological markers of alcohol intake. *Lancet*, 1978; **1**: 978–981.
- ⁷ Whitfield J B, Hensley W J, Bryden D, Gallagher H. Some laboratory correlates of drinking habits. *Ann Clin Biochem* 1978; **15**: 297–303.
- ⁸ Whitfield J B, Hensley W J, Bryden D, Gallagher H. Estimation of alcohol intake from laboratory results. *Ann Clin Biochem* 1978; **15**: 304–306.
- ⁹ Bagrel A, d'Houtaud A, Gueguen R, Siest G. Relations between reported alcohol consumption and certain biological variables in an 'unselected' population. *Clin Chem* 1979; **25**: 1242–1246.

- ¹⁰ Waern U, Boberg J, Hellsing K. Evaluation of indices of alcohol intake in a population of 60-year-old men in Uppsala, Sweden. *Acta Med Scand* 1979; **205**: 353–360.
- ¹¹ Kristenson H, Trell E, Fex G, Hood B. Serum gamma-glutamyl transferase, statistical distribution in a middle-aged male population and evaluation of alcohol habits in individuals with elevated levels. *Prev Med* 1980; **9**: 108–119.
- ¹² Kristenson H, Peterson B, Trell E, Fex G, Larne P, Yettra M. Multiphasic screening in adult males: A comparison of teetotallers with the normal population and with alcohol users. *Am J Clin Nutr* In press.
- ¹³ Gyntelberg F, Meyer J. Relationship between blood pressure and physical fitness, smoking and alcohol consumption in Copenhagen males aged 40–59. *Acta Med Scand* 1974; **195**: 375–380.
- ¹⁴ Klatsky A L, Friedman G D, Siegelau A B, Gérard M J. Alcohol consumption among white, black and yellow men and women: Kaiser Permanente multiphasic health examination data. *Am J Epidemiol* 1977; **105**: 311–323.
- ¹⁵ D'Alonzo C A, Pell S. Cardiovascular disease among problem drinkers. *Occup Med* 1968; **10**: 344–350.
- ¹⁶ Myrhed M. Alcohol consumption in relation to factors associated with ischemic heart disease. *Acta Med Scand* suppl. 1974; 567.
- ¹⁷ Klatsky A L, Friedman G D, Siegelau A S, Gérard M J. Alcohol consumption and blood pressure. Kaiser Permanente Multiphasic Health Examination Data. *N Engl J Med* 1977; **296**: 1194–1200.
- ¹⁸ Beevers D G. Alcohol and hypertension. *Lancet* 1977; **2**: 114–115.
- ¹⁹ Chait A, Mancini M, February A W, Lewis B. Clinical and metabolic study of alcoholic hyperlipidemia. *Lancet* 1972; **2**: 62–64.
- ²⁰ Ostrander L D, Lamphiear D E, Block W D, Johnson B C, Ravenscroft C, Epstein F H. Relationship of serum lipid concentrations to alcohol consumption. *Arch Intern Med* 1974; **134**: 451–456.
- ²¹ Ginsburg H, Olefsky J, Farquhar J W, Reaven G M. Moderate ethanol ingestion and plasma triglyceride levels. *Ann Intern Med* 1974; **80**: 143–149.
- ²² Castelli W P, Gordon T, Hjortland M C, Kagan A, Doyle J T, Hames C G *et al.* Alcohol and blood lipids. The co-operative lipoprotein phenotyping study. *Lancet* 1977; **2**: 153–155.
- ²³ Lieber C S, Davidson C S. Some metabolic effects of ethyl alcohol. *Am J Med* 1962; **33**: 319–327.
- ²⁴ Hed R. Clinical studies in chronic alcoholism II. Carbohydrate metabolism in chronic alcoholism with particular reference to glucose and insulin tolerances. *Acta Med Scand* 1958; **162**: 195–202.
- ²⁵ Lundquist G. Glucose tolerance in alcoholism. *Br J Addict* 1965; **61**: 51–55.
- ²⁶ Rehfeld J F, Juhl E, Hilden M. Carbohydrate metabolism in alcohol-induced fatty liver. *Gastroenterology* 1973; **64**: 445–451.
- ²⁷ Nikkila E, Taskinen M-J. Ethanol-induced alterations of glucose tolerance, postglucose hypoglycemia and bilirubin in serum of chronic alcoholics. *Diabetes* 1975; **24**: 933–943.
- ²⁸ Gérard M J, Klatsky A L, Siegelau A S, Friedman G D, Feldman R. Serum glucose levels and alcohol consumption habits in a large population. *Diabetes* 1977; **26**: 780–785.
- ²⁹ Skude G, Wadstein J. Amylase, hepatic enzymes and bilirubin in serum of chronic alcoholics. *Acta Med Scand* 1977; **201**: 53–58.
- ³⁰ Lindeberg W, Natvig H, Rygh A, Svendsen K. Høyde og vektundersøgelser hos voksne menn og kvinner. Tidskr. *Norsk Laegeforen* 1956; **76**: 361–371.
- ³¹ Comité on enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyl transferase in blood. *Scand J Clin Lab Invest* 1976; **36**: 119–125.
- ³² Schiele F, Guilmin A-M, Detienne H, Siest G. Gamma glutamyl transferase activity in plasma: Statistical distributions, individual variations, and reference values. *Clin Chem* 1977; **23**: 1023–1028.
- ³³ Martin P J, Martin J V, Goldberg D M. Gamma-glutamyltranspeptidase, triglycerides and enzyme induction. *Br Med J* 1975; **1**: 17–18.
- ³⁴ Selzer M L. The Michigan alcoholism screening test. The quest for a new diagnostic instrument. *Am J Psychol* 1971; **127**: 1653–1658.

Accepted for publication 30 December 1979

Alcohol consumption and premature death in middle-aged men

BO PETERSON, HANS KRISTENSON,
NILS H STERNBY, ERIK TRELL,
GÖRAN FEX, BERTIL HOOD

Summary and conclusions

All the men living in Malmö born in 1926-9 were invited for a screening examination which included an assessment of alcohol consumption and measurement of gamma-glutamyltransferase (GGT) activity. They were followed for up to four years (median 2) and their mortality assessed. Sixty-two deaths occurred, 41 (0.9%) among the 4571 men who attended the screening investigation and 21 (1.3%) among the 1609 who did not respond to the invitation. Evidence of alcohol abuse or an alcohol-related cause of death was present in 25 (61%) of the deaths among the attenders and 13 (62%) of those among the non-responders. GGT values at the screening investigation were significantly increased in 19 (46%) of those who died, but established risk factors, such as cholesterol and triglyceride concentrations and blood pressure, had little predictive value.

Measurement of GGT provided an objective index of alcohol consumption, though the full clinical importance of a raised value needs further assessment. The finding that heavy alcohol consumption was the single most

Section of Preventive Medicine, Departments of Internal Medicine, Alcohol Diseases, Pathology, and Clinical Chemistry, University of Lund, Malmö General Hospital, S-214 01 Malmö, Sweden

BO PETERSON, MD, associate researcher in preventive medicine
HANS KRISTENSON, MD, associate researcher in alcohol diseases
NILS H STERNBY, MD, professor of pathology
ERIK TRELL, MD, associate professor of preventive medicine
GÖRAN FEX, MD, associate professor of clinical chemistry
BERTIL HOOD, MD, professor of medicine

important factor associated with premature death in these middle-aged men has important implications for prevention.

Introduction

Though alcohol is recognised to be a major contributory factor in disease and premature death among middle-aged men, the medical profession still tends to underestimate the importance of alcohol in the range of disease.¹ There have been demands for a "public health strategy" to identify and prevent alcohol abuse through screening^{2,3} and for powerful political and economic measures to curb consumption. An important prerequisite for any of these measures is increased knowledge of the medical complications of alcohol consumption.

We established a screening clinic to try to identify and prevent alcohol abuse, and we report here a study on the short-term mortality of middle-aged men who were invited for screening.

Subjects and methods

Screening—A section of preventive medicine was established in autumn 1974 within the medical clinic at Malmö General Hospital. Total male birth-year cohorts in Malmö were invited to a screening investigation, where they underwent measurements of height and weight, pulse rate, blood pressure (standing and recumbent and before and after 10 minutes' rest), and skinfold thickness; simple pulmonary function tests; electrocardiography; and several fasting laboratory estimates, including γ -glutamyltransferase (GGT). All laboratory analyses were performed according to standard methods in the hospital's department of clinical chemistry. GGT was analysed according to the recommendation of the Scandinavian Enzyme Committee.⁴ The usual laboratory upper limit of normal for GGT was 1.0 μ kat/l, but in our screening clinic we used 1.44 μ kat/l as a cut-off limit for further investigation. Attenders were also asked to fill in a questionnaire on their alcohol intake. Findings at the screening investigation were checked one or two weeks later and if confirmed the patient was invited for further investigation and treatment at special outpatient clinics within the department of preventive medicine. These included clinics for blood pressure, lipids, "borderline diabetes," and raised GGT values.⁴

Study of population—Screening started in November 1974 with men born in 1926. Subsequent birth-year cohorts of men were examined consecutively in the following years together with women and a few younger birth-year cohorts. At the end of 1978 all men living in Malmö who were born in 1926-9 had been invited for screening—a total of

6180. Of these; 4571 (74%) responded. All the men were aged 48 or 49 years at the screening investigation, and they were followed-up for up to four years (median two years).

Mortality—Information on deaths occurring after the invitation to screening in these birth-year cohorts was obtained from a register at the department of pathology, Malmö General Hospital. This register covers all deaths in Malmö, including those where necropsy is not performed. There were 41 (0.9%) deaths among the 4571 men who attended for screening and 21 (1.3%) among the 1609 who did not. The necropsy rate was 90% (36/41) among attenders and 100% among the non-responders.

Alcohol consumption—To assess the part that alcohol consumption may have played in each death all accessible information on the deaths was reviewed: protocols from screening death certificates, necropsy reports, police reports, and hospital records, including those of the alcohol clinic of Malmö General Hospital. The men who died were classified as having an alcohol-positive history if this information showed at least one of the following: (a) a history of heavy alcohol consumption; (b) registration at the alcohol clinic; (c) a raised GGT value at the screening investigation which, after interview with one of us (HK), was considered to be due to heavy drinking.⁴ Those men who did not fulfill these criteria included a few who had only scanty or inconclusive information. All deaths from medical complications of alcoholism—for example, cirrhosis of the liver, oesophageal varices, and alcohol intoxication—and cases where alcohol intoxication contributed to the death according to necropsy reports were classified as probable alcohol-related deaths. Deaths from conditions that may have been related to alcohol consumption were classified as possible alcohol-related deaths.

Results

Table I shows causes of death, GGT values, and histories of alcohol consumption and smoking in the attenders at the screening clinic. Nineteen men had raised GGT activities and 21 a history of heavy alcohol consumption. These findings are related to the main causes of death in table II: raised GGT values and history of alcohol consumption were particularly prominent among men who committed suicide or died in accidents and those who died of miscellaneous causes (which included cirrhosis of the liver, bleeding oesophageal varices, etc).

Table III shows the causes of death according to the death certificates and a retrospective classification of alcohol consumption among non-responders. Mortality after the date of invitation to screening among non-responders was almost one and a half times that among attenders (1.3% compared with 0.9%). A directly alcohol-related cause of death was found in 10 of the 21 cases and a positive history of heavy alcohol consumption in 13 (62%).

There was a lower incidence of cardiovascular deaths, a higher

Case No	Cause of death	GGT ($\mu\text{kat/l}$)	History of heavy alcohol intake	History of smoking	Other screening findings*	Time between investigation and death (yr)	Alcohol-related death
1	Malignant glioma	0-42	-	+	BP (diastolic) 105 mm Hg	1	
2	Cardiac hypertrophy, alcohol intoxication	1-93	+	+		2	Probable
3	Alcohol and barbiturate intoxication	2-33	+	+		1	Probable
4	Malignant histiocytosis	2-98	+	+		1	Possible
5	Pancreas cancer	1-84	+	+	Triglyceride 3.5 mmol/l, relative body weight 1.4	1	Probable
6	Alcohol intoxication	8-14	+	+		1	
7	Train accident (engine-driver)	2-42	+	-		1	Possible
8	Ethanol and hexapropylmate intoxication	0-82	+	+		1	Probable
9	Cor pulmonale	0-46	-	NA	PF 2.1/l/min, FVC 0.7 l	2	Probable
10	Suicide (car exhaust)	0-60	-	+	Relative body weight 2.2	1 1/2	
11	Liver cirrhosis, chronic alcoholism	1-77	-	+	ESR > 100 mm in 1 h	2	Probable
12	Bronchial cancer	1-44	-	NA		2 1/2	Probable
13	Alcoholic cardiomyopathy	1-11	+	+	Hb 114 g/dl, glucose 8.6 mmol/l	2	Probable
14	Pancreatitis	1-11	+	+		2	
15	Diffuse abdominal adenocarcinoma	3-22	+	+		2	Probable
16	Pulmonary embolism	0-30	+	+		2	
17	Mycocardial infarction	0-74	-	+		1 1/2	Probable
18	Mycocardial infarction	1-94	-	+		1	
19	Liver cirrhosis	31-7	+	+	Hb 106 g/dl, ESR 89 mmol/l	1	Probable
20	Mycocardial fibrosis	0-91	+	+	Relative body weight 1.4, glucose 7.9 mmol/l	1	
21	Pulmonary embolism	1-58	+	NA	Glucose 7.2 mmol/l	1	Probable
22	Duodenal rupture (traumatic ?)	0-79	+	+	BP 215/135 mm Hg	1	Probable
23	Dissecting aortic aneurysm	0-53	-	+		1	
24	Mycocardial infarction	1-86	+	+		3	Possible
25	Pancreatic neoplasm	0-47	+	+		4	
26	Coronary sclerosis	0-35	+	+		3	
27	Chronic myeloid leukaemia	5-15	-	+		3	
28	Cardiosclerosis, diabetes	1-93	?	-	W/B 59 $\times 10^9/l$	3	
29	Malignant melanoma	0-84	+	NA	Triglyceride 3.1 mmol/l, glucose 7.3 mmol/l	2	
	Systemic hypertension	1-65	+	+	1.5; creatinine 438 $\mu\text{mol/l}$	2	
30	Bronchial cancer	0-72	-	+	BP 220/150 mm Hg, relative body weight 1.5; creatinine 438 $\mu\text{mol/l}$	2 1/2	
31	Pancreatic neoplasm	0-79	-	+	Relative body weight 1.4	2	
32	Cardiosclerosis	0-75	-	-	BP 170/115 mm Hg	2	
33	Myelitis, myocarditis	0-33	-	+	BP 190/115 mm Hg, relative body weight 1.6	3	
34	Cerebral haemorrhage	0-60	-	+	BP 155/110 mm Hg	2 1/2	
35	Mycocardial infarction	1-33	-	+		2	
36	Cardiosclerosis	2-59	+	+		2	
37	Cardiosclerosis	0-56	+	+	BP 165/115 mm Hg	2	
38	Bleeding oesophageal varices	2-96	+	-	BP 175/105 mm Hg, glucose 8.2 mmol/l	1 1/2	Probable
39	Bronchopneumonia	3-19	+	+	Triglyceride 3.1 mmol/l, glucose 9.0 mmol/l	1	Possible
40	Mycocardial infarction	0-44	+	+	Operated angina pectoris 1966	1	
41	Mycocardial infarction, diabetes	0-56	-	+	Known diabetes with complications	2	

*Recumbent blood pressure (BP) was measured after 10 minutes' rest. Relative body weight = actual weight/ideal weight for age, sex, and height. PF = Peak flow. FVC = Forced vital capacity. ESR = Erythrocyte sedimentation rate. Glucose value was that measured at 120 minutes during glucose tolerance test. W/B = White blood count. Conversion: *SI to traditional units*—GGT: 1 $\mu\text{kat/l} \approx 60$ iu/l. Triglyceride: 1 mmol/l ≈ 89 mg/100 ml. Glucose: 1 mmol/l ≈ 18 mg/100 ml.

incidence of alcohol-related deaths, and a higher incidence of attendance at the alcoholic clinic among the non-responders than among those who attended the screening clinic (table IV). Nevertheless, over half the attenders had a history of heavy alcohol consumption and about half had raised GGT activities. Altogether 25 (61%) of the attenders had a history of alcohol consumption or raised GGT values, or both.

Table V shows that the premature deaths among attenders were

TABLE II—*Causes of death among participants and non-responders according to GGT activities and alcohol history*

	Participants			Non-responders		Total	
	No	No with raised GGT	No with history of heavy alcohol intake	No	No with history of heavy alcohol intake	No	No with history of heavy alcohol intake
Cardiovascular diseases	15	6	6	5	4	20	10
Cerebrovascular diseases	1	0	0	2	1	3	1
Miscellaneous causes ..	10	6	8	9	5	19	13
Malignant neoplasms ..	10	4	3	1	1	11	4
Suicide/accidents ..	5	3	4	4	2	9	6
Total ..	41	19	21	21	13	62	34

TABLE III—*Causes of death and history of alcohol consumption in non-responders*

Case No	Cause of death	Time between investigation and death (yr)	Alcohol history	Alcohol related death
1	Pulmonary embolism, pancreatitis	2 mnth	+	Probable
2	Pulmonary embolism	2	—	
3	Cardiac hypertrophy	1	+	Probable
4	Dissecting aortic aneurysm	$\frac{1}{2}$	—	
5	Myocardial infarction	$\frac{1}{2}$	+	
6	Myeloid leukaemia	1 mnth	—	
7	Burn injury, alcohol intoxication	$\frac{1}{2}$	+	Probable
8	Myocardial infarction	1 mnth	+	
9	Cerebral haemorrhage, diabetes mellitus	3	—	
10	Accidental drowning	2	—	
11	Pneumonia, myelopathy	2	—	
12	Hepatic cirrhosis	2	+	Probable
13	Colonic carcinoma	2	+	
14	Hepatic cirrhosis	2 $\frac{1}{2}$	+	Probable
15	Respiratory insufficiency	2	—	
16	Suicide, depression	2	—	
17	Ventricular ulcer with haemorrhage	1	+	Probable
18	Subdural haematoma	1 $\frac{1}{2}$	+	"
19	Myocardial fibrosis, alcohol intoxication	1	+	"
20	Drowning, alcohol intoxication	$\frac{1}{2}$	+	"
21	Oesophageal varices	$\frac{1}{2}$	+	"

TABLE IV—Comparison between attenders and non-responders. Results are numbers of subjects

	Participants	Non-responders	Total
Relative mortality	0.9% (1)	1.3% (1.45)	1%
Raised screening GGT (≥ 1.4) ..	19/41		
Known at alcohol clinic	11/41	9/21	20/62 (32%)
Alcoholic history	21/41	13/21	34/62 (55%)
Probable alcohol-related death ..	12/41	10/21	22/62 (36%)
Possible alcohol-related death ..	4/41		
Necropsy	36/41	21/21	57/62 (92%)

TABLE V—Numbers of deaths among participants according to GGT activities, serum cholesterol and triglyceride concentrations, recumbent diastolic blood pressure after 10 minutes' rest, and serum urate values. Quintiles are derived from distribution of values among all participants screened in 1926-9 birth-year cohorts ($n=4571$)

GGT (μ kat/l)	≤ 0.4	-0.52	-0.67	-0.96	≥ 0.97
No of deaths	3	5	4	9	20
Cholesterol (mmol/l)	≤ 5.0	-5.5	-6.1	-6.8	≥ 6.9
No of deaths	12	11	7	5	6
Triglyceride (mmol/l)	≤ 1.0	-1.25	-1.50	-2.02	≥ 2.03
No of deaths	13	3	5	10	9
Diastolic blood pressure (mm Hg)	≤ 75	-85	-90	-95	≥ 96
No of deaths	6	12	10	2	11
Urate (μ mol/l)	≤ 257	-292	-322	-358	≥ 359
No of deaths	5	8	3	10	15

concentrated in those whose GGT values were in the upper quintiles of the distribution of values among the whole population screened. A similar correlation did not exist for other values commonly regarded as risk factors (table V), though there was a slight tendency for those who died to have serum urate values in the upper quintiles; urate concentrations may also correlate with alcohol consumption.⁴

Discussion

In this unselected population of Swedish urban men alcohol was the most important single factor associated with death at about the age of 50: an alcohol-positive history was present in over half the men who died. Our study was a short-term prospective study of mortality in a fairly large population, uniform for age and sex, who were invited for screening and followed for up to four years (median two years). Our analysis of alcohol consumption was partly prospective and partly retrospective.

Many studies have confirmed the general impression that alcoholics have increased morbidity and mortality,^{1,2,5-8} and such features should also be identified in population studies.

Nevertheless, few population studies have been performed because of the difficulties of measuring alcohol consumption. Reliance on self-reported consumption in questionnaires makes findings open to doubt. At our screening investigation we used a modified Michigan alcoholism screening test,^{3,4} but we also used a biochemical index of heavy alcohol consumption.

With methods partly comparable to ours Tibblin studied 2992 men living in Gothenberg who were born in 1913.⁵⁻⁷ He found that of the 273 who died aged 35-55 17% were heavy drinkers or died from alcohol-related conditions.⁷ Lannerstad examined 49 deaths that occurred among 802 men in Malmö at the age of 55-60 years; in 27% he found signs of alcohol abuse, defined as registration at the alcohol clinic or a blood alcohol concentration at necropsy of more than 22 mmol/l, or both.⁸ The American epidemiological studies in Framingham and at Chicago Western Electric Company also showed an association between alcohol consumption and all causes of death,^{9,10} but comparisons are difficult because these populations were selected and the ages were different.

Serum GGT activity has been shown in series of alcoholics¹¹⁻¹³ and in population studies^{4,14-17} to be the best single biochemical index of high alcohol consumption. Nevertheless, the clinical significance of raised activities has still not been assessed. Measurement of GGT activity may play a useful part in screening investigations for alcohol abuse, especially in middle-aged men. We have already shown that 75% of those with raised GGT values can be classified as heavy users of alcohol.⁴ Our present results illuminate the question of clinical significance by showing that the risk of dying was six to seven times greater in men with GGT values in the highest quintile than in those with values in the lowest quintile. It remains to be seen whether the heavy consumer of alcohol with a normal serum GGT value on screening has a better outlook.

Interestingly, a high serum cholesterol value appeared to be an inverse risk factor for premature death—a finding supported by other reports.^{8,18} In a mortality study with a short follow-up such as ours some individuals may have already been ill and in poor nutritional state at the time of the examination, but the relationship between cholesterol concentration and premature death merits further consideration. It is hard to evaluate the role of smoking in our cohorts; 70% of the 41 attenders who died were smokers, and they were concentrated in the subgroup with a history of heavy alcohol consumption. This probably reflects the known association between alcohol consumption and smoking.

An assessment of drinking habits is a relevant aim in population investigations of middle-aged men, and measurements of

serum GGT may help if coupled with a clinical evaluation and treatment programme. Although our observations on short-term mortality permit no certain general epidemiological conclusions at this stage, we think that our findings are clear and relevant and carry important implications for prevention.

This study was supported by the Swedish Council for Planning and Co-ordination of Research (BP) and the Swedish Delegation for Social Research, Ministry of Health and Social Affairs (HK).

References

- ¹ Straus R. Alcohol abuse and physicians' responsibility. *Arch Intern Med* 1977;**137**:1513-5.
- ² Lieber CS. A public health strategy against alcoholism and its complications. *Am J Med* 1978;**65**:722-6.
- ³ Selzer ML. The Michigan alcoholism screening test (MAST): the quest for a new diagnostic instrument. *Am J Psychiatry* 1971;**127**:1653-8.
- ⁴ Kristenson H, Trell E, Fex G, Hood B. Serum gamma-glutamyltransferase: statistical distribution in a middle-aged male population and evaluation of alcohol habits in individuals with elevated levels. *Prev Med* 1980;**9**:108-19.
- ⁵ Tibblin G. High blood pressure in men aged 50. *Acta Med Scand* (Suppl) 1967;**470**.
- ⁶ Tibblin G. Alkohol som riskfaktor för sjukdom och död. *Läkartidningen* 1974;**71**:2053-5.
- ⁷ Tibblin G, Wilhelmsen L, Werkö L. Risk factors for myocardial infarction and death due to ischaemic heart disease and other causes. *Am J Cardiol* 1975;**35**:514-22.
- ⁸ Lannerstad O. Död och sjukdom bland medelålders män. Thesis. *Studentlitteratur (Lund)* 1978.
- ⁹ US Secretary of Health, Education and Welfare. *Second special report to the US Congress on alcohol and health*. Washington: US Department of Health, Education and Welfare, 1974. (Preprint edition.)
- ¹⁰ Dyer RD, Stamler J, Paul O, et al. Alcohol consumption, cardiovascular risk factors and mortality in two Chicago epidemiologic studies. *Circulation* 1977;**56**:1067-74.
- ¹¹ Rosalki SB, Rao D. Serum gamma-glutamyltranspeptidase activity in alcoholism. *Clin Chim Acta* 1972;**39**:41-7.
- ¹² Rollason JG, Pincherle G, Robinson D. Serum gamma-glutamyltranspeptidase in relation to alcohol consumption. *Clin Chim Acta* 1972;**39**:75-80.
- ¹³ Wu A, Slavin G, Levi AJ. Elevated serum gamma-glutamyltransferase (transpeptidase) and histological liver damage in alcoholism. *Am J Gastroenterol* 1976;**65**:318-23.
- ¹⁴ Whitehead TP, Clarke CA, Whitfield AGW. Biochemical and haematological markers of alcohol intake. *Lancet* 1978;**i**:978-81.
- ¹⁵ Whitfield JB, Hensley WJ, Bryden D, Gallagher H. Some laboratory correlates of drinking habits. *Ann Clin Biochem* 1978;**15**:297-303.
- ¹⁶ Bagrel A, d'Houtard A, Gueguen R, Siest G. Relation between reported alcohol consumption and certain biological variables in an "unselected" population. *Clin Chem* 1979;**25**:1242-6.
- ¹⁷ Kondo H, Hashida M, Momotani H. Serum gamma-glutamyltranspeptidase as a diagnostic aid in the periodic health examination. *Sangyo Igaku* 1976;**1**:95-100.
- ¹⁸ Beagelhole R, Foulkes MA, Prior IAM, Eyles EF. Cholesterol and mortality in New Zealand Maoris. *Lancet* 1980;**ii**:285-7.

(Accepted 6 March 1980)

Public Health

ALCOHOL-RELATED DEATH: A MAJOR CONTRIBUTOR TO MORTALITY IN URBAN MIDDLE-AGED MEN

BO PETERSSON
HANS KRISTENSSON

PETER KRANTZ
ERIK TRELL

NILS H. STERNBY

Section of Preventive Medicine, Department of Internal Medicine, and Departments of Forensic Medicine and Pathology, University of Lund, Malmö General Hospital, Malmö, Sweden

Summary The role of alcohol abuse in mortality was studied in an unselected population of over 10 000 46–48-year-old men in Malmö, Sweden. During follow-up of 0–6 years (mean 3 years) 199 men died. In 61 men (30.7%) death was alcohol related. A theoretical calculation of excess deaths in men with an alcohol-positive history yielded 78 deaths (39.2%). In the official cause of death statistics 10 of the deaths had been assigned alcoholic aetiology (5.0%). These estimates indicate that alcohol was the commonest underlying factor in death in this sample of middle-aged men. The number of deaths with alcoholic aetiology in official cause of death statistics should be multiplied by a factor of six to eight to arrive at the true alcohol-related death rate.

INTRODUCTION

MOST studies of the role of alcohol in mortality are based on official statistics which are a deficient source because they tend to underestimate the frequency of alcohol-related deaths. A theoretical calculation of this under-reporting was made by Hackl.¹ We have attempted to analyse the under-reporting in detail for deaths in middle-aged men in the Malmö Preventive Programme.

SUBJECTS AND METHODS

Population

Details of the Malmö Preventive Programme have been published elsewhere.^{2,3} Total birth-year cohorts of middle-aged men were invited to a health screening. For the purposes of the present study the birth-year cohorts 1926–32, examined in 1975–79, were included. Of the 10 353 men in these cohorts invited, 7725 (74.6%) participated in the screening. These men were 46–48 years old at screening, or at invitation to screening.

The screening procedure was followed by an intervention programme for hypertension, hyperlipidaemia, impaired glucose tolerance, overweight, and complications of tobacco use and alcohol consumption. One of the aims of the programme was to investigate the practicability of using the serum enzyme gamma

glutamyltransferase (S-GT) for the detection of and in continuous control of alcohol-related problems.³ Men with higher than normal levels of S-GT were randomly allocated to control and intervention groups.³

Mortality

The mortality after screening, or after appointment for screening in the case of the non-participants, was followed for 1975–80, a follow-up time of 0–6 years (mean 3 years). The mean age of death was 50 years. All deaths in Malmö residents are registered at the department of pathology, and from this file deaths in men in the analysed cohorts were identified. For the dead subjects information was collected from all available sources: screening protocols, hospital records, necropsy reports, police records, and death certificates. Most necropsies on men dying in hospital were done at the department of pathology, and those for men dying outside hospital were done at the department of forensic medicine. In Sweden a forensic necropsy is done at the request of the police for violent or unexpected or unexplained deaths.

Alcohol-positive History

By studying all available information a revised cause of death was established, and the history of alcohol use was investigated. If a subject was registered at the department for alcoholic diseases (DAD), or if any other source of information indicated alcohol abuse, he was labelled as having an alcohol-positive history (APH). The presence of alcohol in the blood at forensic necropsy was also noted.

Alcohol-related Death

We created a cause of death category, "alcohol-related death": a death was included in this category if high alcohol consumption was considered the major underlying cause in the chain of events leading to the death. In this study the following subgroups were identified.

Accidents were defined as accidental deaths occurring in an alcohol-intoxicated state. Almost all occurred in known alcoholics.

Organic deaths were caused by an organic complication of alcoholism in an alcoholic—e.g., liver cirrhosis, pancreatitis, and cardiomyopathy.

Suicide in a known alcoholic.

Pneumonia in a known alcoholic.

Cause unknown in a known alcoholic.

Intoxication.—Under this heading we included deaths in known alcoholics, most of whom were found dead, all with alcohol in the blood or urine at necropsy, and with no other specific cause of death demonstrable, such as myocardial infarction, cancer, or haemorrhage.

Cause of Death Statistics

The underlying causes of death according to the 8th International Classification of Diseases⁴ were recovered from the Swedish Central Bureau of Statistics. In this classification, alcohol is explicitly stated as the cause of death in E860.000 (alcohol intoxication), 291 (alcohol psychosis), 303 (alcoholism), and 571.00 (alcoholic cirrhosis of the liver). However, in this classification many cases of supposedly non-alcoholic liver cirrhosis do have alcoholic aetiology, as do cases of pancreatitis (577).

RESULTS

During the study period 199 men died, and they form the study group. Necropsy was carried out for 175 men (87.9%). 16 of 111 deaths in men whose necropsy was done in the department of pathology or who had no necropsy (fig. 1) were alcohol related (14.4%). Liver cirrhosis was the cause of death in 12 of these. 33 (29.7%) had an APH, and 21 (18.9%) were known at the DAD.

In the forensic-necropsy group (fig. 2) 45 of 88 deaths were classified as alcohol related (51.1%). Alcohol was present in

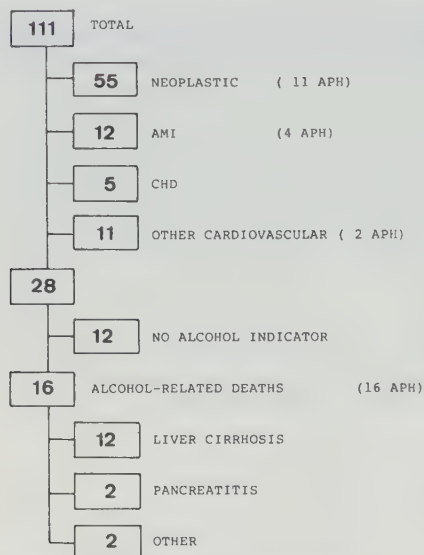


Fig. 1—In-hospital-necropsy and no-necropsy deaths (n = 111).

APH = alcohol-positive history; AMI = acute myocardial infarction; CHD = coronary heart disease; alcohol indicator = APH and/or alcohol-related death (blood ethanol was not analysed, but was not expected to be found in any case).

the blood at necropsy in 26 cases (29.5%) and in 1 subject it was found only in the urine. The blood alcohol concentrations ranged from 0.2 to 3.1 promille (20–310 mg/100 ml). 59 cases (67.0%) had an APH, and 44 (50.0%) men were registered at the DAD.

In all, 61 of the 199 deaths (30.7%) were classified as alcohol related. This category was thus a major mortality category in this population, and alcohol-related deaths were more common than deaths due to cancer or cardiovascular diseases. 92 subjects (46.2%) had an APH, and 65 (32.7%) were registered at the DAD.

Intoxication accounted for 19 of the 61 alcohol-related deaths (31.3%). The blood alcohol concentrations in this group ranged from 0.2 to 2.9 promille (20–290 mg/100 ml); 1 subject had alcohol in the urine only. Many subjects had combinations of intoxication with alcohol and sedatives, hypnotics, and other drugs. Varying degrees of myocardial fibrosis, coronary atherosclerosis, or both were found at necropsy. The exact part played by any one of these factors in causing the death was difficult to establish. It was also unclear whether in some cases there was suicidal intent. Cirrhosis of the liver accounted for 16 deaths—i.e., 26.2% of all alcohol-related deaths. 1 of these subjects also had an α_1 -antitrypsin deficiency. 1 non-alcoholic man died of (biliary) liver cirrhosis. Thus, 16 of 17 deaths from liver cirrhosis (94.1%) occurred in alcoholics. 9 alcohol-related deaths were due to accidents, 3 to pneumonia, 6 to suicide, 6 to other organic causes, and the cause was unknown in 2.

In the official cause of death statistics (see table), only 4 of the 16 cases of alcoholic liver cirrhosis were assigned an alcoholic aetiology (571.00). 5 deaths were coded as alcohol intoxication (E 860.00) and 1 as alcoholism (303.20). Altogether, 10 of 61 cases were correctly coded as alcohol related, an under-reporting of about 5 out of 6 cases. If all deaths from liver cirrhosis,¹¹ pancreatitis,² and oesophageal

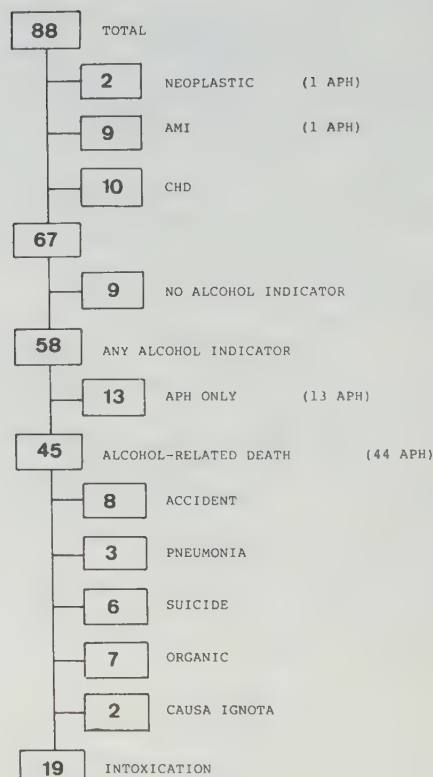


Fig. 2—Forensic-necropsy deaths (n = 88).

For abbreviations, see fig. 1. Alcohol indicator = APH, blood or urine ethanol at necropsy, alcohol-related death, or a combination. Organic deaths: 4 from cirrhosis and 3 from other causes.

varices (456.00, 1 death) are added, 24 deaths (12.1%) are included (see table).

To investigate whether the size of the alcohol-related-death category was an exaggeration of the role of alcohol abuse as a cause of death, a theoretical estimate of the magnitude of this role was made. The study population comprised 10 353 men, of whom 808 (7.8%) were registered at the DAD. 65 of these died during follow-up, a death rate of 8.0%. Another 27 deaths occurred in men with an APH, but these men were not known at the DAD. If we assume that the APH group had the same death rate as the DAD group, the whole group with an APH may have consisted of 1146 men. The population without an APH thus had a death rate of 1.2% during the follow-up period (107 deaths). The death rate in the APH, DAD-registered group was thus 6.8 times that in the men with no history of alcohol abuse.

If the APH group had had the same death rate as the non-alcoholic population, 13.8 men would have died—i.e., there

COMPARISON OF ESTIMATES OF THE PART PLAYED BY ALCOHOL IN 199 DEATHS IN MIDDLE-AGED MEN

Method	No.	% of total
Alcohol-related-death category	61	30.7
Calculation of excess deaths in men with APH	78	39.2
Official statistics:		
E 860.00; 571.00; 303.20 only	10	5.0
E 860.00; 571.00; 303.20 plus 571.90; 456.00; 577	24	12.1

was an excess of 78 deaths in the APH population (92 deaths actually occurred). This figure of 78 deaths should be compared with our earlier estimate of 61 deaths as alcohol related.

This calculation assumes that all excess deaths due to alcohol abuse occurred in the APH population.

DISCUSSION

We have attempted to evaluate the extent of alcohol abuse as a cause of death in an unselected population, not using official statistics or self-reporting of alcohol consumption habits. In men who died at around the age of 50 years in this study, alcohol-related causes of death formed the largest mortality category and accounted for about a third of all deaths. This estimate corresponded quite well with a theoretical estimate, but it was six times higher than official statistics indicated. This under-reporting has been pointed out by others.^{5,6}

Despite the arbitrariness of the definition of the category alcohol-related deaths, even our total probably underestimates the true extent of alcohol abuse in death for many reasons. In some subjects for whom scanty data were available, alcohol abuse may have been an important factor. Also, we did not consider death from cancer, myocardial infarction, stroke, or other specific cardiovascular disease to be alcohol related, although alcohol has been incriminated as one aetiological factor in these diseases.⁷⁻¹¹ However, the mode of death in subjects with moderate alcohol concentrations in the blood at necropsy may have been cardiac arrhythmias.¹² The effects of intervention against heavy drinking in the participants with high levels of S-GT may also have reduced the number of alcohol-related deaths, and preliminary results indeed indicate a slight effect of intervention on mortality (unpublished).

Usually, analyses of the role of alcohol abuse in mortality are undertaken in selected populations, such as cohorts of alcoholics,¹³⁻¹⁶ but we think it important to study unselected populations in order, for instance, to monitor effects of public health measures.

The extent of alcohol abuse as a cause of death in this group necessitates a search for objective methods¹⁷ to identify alcohol-related health problems in order to institute preventive measures, as have been suggested by Lieber,¹⁸ and which are attempted in the Malmö Preventive Programme.³

This study was supported by the Swedish Council for Planning and Coordination of Research.

Correspondence should be addressed to B. P., Section of Preventive Medicine, Department of Internal Medicine, Malmö General Hospital, S-214 01 Malmö, Sweden.

REFERENCES

1. Hackl H. Untersuchungen zur Ermittlung der wahren Alkoholismuserblichkeit. *Deutsch Med Wochr* 1980; **105**: 1343-47.
2. Petersson B, Kristensson H, Sternby NH, Trell E, Fex G, Hood B. Alcohol consumption and premature death in middle-aged men. *Br Med J* 1980; **280**: 1403-06.
3. Kristensson H, Trell E, Hood B. Serum gamma glutamyltransferase in screening and continuous control of heavy drinking in middle-aged men. *Am J Epidemiol* 1981; **114**: 862-72.
4. World Health Organisation. International classification of diseases, injuries, and causes of death (ICD). 8th revision, 1965. Geneva: WHO, 1967.
5. Valverius M. Alcohol and mortality. Skandia International symposia. Stockholm: Almqvist & Wiksell, 1980: 314-25.
6. Nashold RD, Naor EM. Alcohol-related deaths in Wisconsin: the impact of alcohol on mortality. *Am J Public Health* 1981; **71**: 1237-41.
7. Lieber CS, Seitz HK, Garro AJ, Worner TM. Alcohol-related diseases and carcinogenesis. *Cancer Res* 1979; **39**: 2863-86.

References continued at foot of next column

B. PETERSSON AND OTHERS: REFERENCES—continued

8. Tibblin G, Wilhelmsson L, Werkö L. Risk factors for myocardial infarction and death due to ischaemic heart disease and other causes. *Am J Cardiol* 1975; **38**: 514-22.
 9. Ashley MJ, Rankin JG. Hazardous alcohol consumption and diseases of the circulatory system. *J Stud Alcohol* 1980; **41**: 1040-70.
 10. Fraser GE, Upadell M. Alcohol and other discriminants between cases of sudden death and myocardial infarction. *Am J Epidemiol* 1981; **114**: 462-76.
 11. D'Alonzo CA, Pell S. Cardiovascular disease among problem drinkers. *J Occup Med* 1968; **10**: 344-50.
 12. Eitinger PO, Wu CF, De La Cruz C, Weisse AB, Ahmed SS, Regan TJ. Arrhythmias and the "holiday heart": alcohol-associated cardiac rhythm disorders. *Am Heart J* 1978; **95**: 555-62.
 13. Sundby P. Alcoholism and mortality. Oslo: Universitetsforlaget, 1967.
 14. Schmidt W, DeLint J. Cause of deaths in alcoholics. *Quart J Stud Alcohol* 1972; **33**: 171-85.
 15. Thorarinnsson AA. Mortality among men alcoholics in Iceland 1951-74. *J Stud Alcohol* 1979; **40**: 704-18.
 16. Nicholls P, Edwards G, Kyle E. Alcoholics admitted to four hospitals in England. II. General and cause-specific mortality. *Quart J Stud Alcohol* 1974; **35**: 841-55.
 17. Editorial. Screening tests for alcoholism? *Lancet* 1980; **ii**: 1117-18.
 18. Lieber CS. A public health strategy against alcoholism and its complications. *Am J Med* 1978; **65**: 722-26.
-

MAJOR DETERMINANTS OF PREMATURE MORTALITY IN URBAN
MIDDLE-AGED MALES

Alcohol-related deaths and degree of participation in
a preventive population program against alcohol and
its complications.

Bo Petersson, Erik Trelle, Peter Krantz and Bertil Hood.

From the Section of Preventive Medicine, Departments
of Internal Medicine and Forensic Medicine, University
of Lund, Malmö General Hospital, S-214 01 Malmö,
Sweden.

This study was supported by the Swedish Council for
Planning and Coordination of Research, AFA (Arbets-
marknadens Försäkringsaktiebolag) and Kristianstads
Läns Landsting.

ABSTRACT

The total, consecutive mortality in a population of 10 353 middle-aged males invited to a preventive medical population program in Malmö was followed up 1.5-6.5 years, mean 4.5 years, after the time of invitation and analysed in relation to participation or non-participation, forensic or in-hospital autopsy and possible intervention effects. The total mortality was twice as high in the non-participants as in the participants, and the death rate due to alcohol-related diseases five times higher. There were no significant differences in the other death causes; cancer, cardiovascular deaths or others. In the non-participants autopsied at the Forensic Department the proportion of alcohol-related deaths was 60.5%, in comparison with 10.0% in participants autopsied in hospital. A history of alcohol abuse was present in 45.2% of the total, and in 61.0% of the forensic mortality material. In participants with increased screening gamma-glutamyltransferase (GGT), mortality at 48-72 months' follow-up was lower in an intervention group in comparison with a control group matched for sex, age and GGT. The results support that alcohol-related deaths, non-participation in a preventive population program, and intervention effects in a public health strategy against alcohol and its complications are major determinants of premature mortality in middle-aged urban males.

INTRODUCTION

Lieber has proposed a "public health strategy against alcoholism and its complications" (1). The major role that alcohol plays in morbidity and mortality in western societies is often underestimated because alcohol-related mortality is underreported in official statistics (2-4).

A public health strategy is dependent upon a response in the population, and non-participation in preventive programs could be considered as a risk factor for alcohol-related disabilities. In Sweden, this issue has been studied by Tibblin (5) who states that a "negative attitude towards medical care" was the main reason for non-participation. Wilhelmsen et al. (6) reported a mortality three times higher in non-participants than in participants, and a higher rate of alcoholism in the dead non-participants at follow-up.

In a previous report we tried to quantitate the underestimation of alcohol-related mortality in our population (2). When the Malmö Preventive Program started in 1974, one of its aims was to investigate methods of intervention for heavy drinking and alcohol-related health problems (7,8). The mortality has been followed up continuously in all the population groups invited to participate in the program. The purpose of the present report is to describe the results in the total follow-up material with particular reference to the magnitude of alcohol-related deaths, the different mortality patterns and modes of death in participants as compared to non-participants, and to consider possible effects of the intervention.

METHODS

Study population

The Malmö Preventive Program in middle-aged men started in 1974 and is still going on. Beginning with the men born in 1926, total birth-year cohorts of men living in Malmö, Sweden, were invited to a multiphasic health screening followed by intervention. The present study involves the cohorts born 1926-1932; 10 353 men in all. All males were successively examined between 1st of September 1974 and 30th of June 1979, when they were 46-48 years old. All inhabitants in Sweden have a national registration number of 10 digits, composed of the date of birth, three ordering digits and one check digit. Names,

addresses and registration numbers for all invited were accessible from the official county census bureau. Of the invited 10 353 men, 7 725 participated (74.6%[§]). Thus, 2 628 were non-participants[§].

Screening investigation and intervention.

All screening investigations were performed in the morning after an overnight fast. Venous blood samples were obtained in the supine position after 10 minutes rest. The investigation included: measurement of weight, height (from which a relative weight/height index was calculated), skinfold thickness, pulse rate at 0 and 10 minutes, standing and recumbent systolic and diastolic blood pressures at 0 and 10 minutes, simple pulmonary function tests, an electrocardiogram, an oral glucose tolerance test (OGTT), several biochemical analyses (8,9). The screening investigation also included a questionnaire with questions on heredity, smoking, medical history, physical activity etc (9), and on attitude towards alcohol (10).

Abnormal screening findings were intervened upon at the Department of Preventive Medicine. Special out-patient clinics were organized for hypertension, hyperlipidemia, overweight, smoking, borderline glucose tolerance and elevated values of serum gamma glutamyl-transferase (GGT) (7,8). Half of the subjects with GGT in the upper decile of the screening distribution (≥ 1.4 ukat/l), confirmed at a repeat test, were on random basis assigned to a controlled intervention program (7,8). The results of this out-patient clinic have now been followed up for between 48-72 months (11,12).

Registration and analysis of mortality.

Records of deaths among the screened population up to the end of 1981, a follow-up time of 1.5-6.5 years (mean 4.5 years), were obtained from the Department of Pathology, Malmö General Hospital, which is notified of all deaths in Malmö residents. In order to estimate the number of deaths in men after having moved from the town or been lost to follow-up, original invitation files were matched to the actual registers for the same cohorts at the

[§] We have found that about 10% of the non-participants may not have been reached by the letter of invitation because of wrong addresses due to moving or inaccuracy of census information.

official census bureau by mid-1981. For all subjects not remaining in the town, according to this matching, a nationwide manual search was undertaken. In this way only 65 men of 10 353 were lost to follow-up (0.6%) and 47 of these had emigrated. This loss is ignored in the calculations. A few deaths outside Malmö were identified and these are included in the analyses.

For the dead subjects all accessible documentation was analysed (viz. screening protocols, hospital records, autopsy reports, forensic autopsy reports, police protocols and death certificates) and a (revised) cause of death formulated (2). The majority of the deaths were autopsied (see table III): hospital deaths at the Department of Pathology, deaths outside hospital at the Department of Forensic Medicine. The place of death in itself reflects different patterns of death. Forensic autopsy is, in Sweden, performed at the request of the police in cases of violent or otherwise unexpected/unexplained deaths.

Indicators of possible role for alcohol as contributory or causative factor for death.

Indicators of possible role for alcohol were of four kinds,

1. Registration at the Department of Alcohol Diseases
2. Information from other sources, mainly police protocols, that a subject was an "abuser" of alcohol.
3. Elevated screening GGT, at interview considered to be due to alcohol consumption.

If one or more of these three indicators were present for a dead subject, the subject was said to have an "alcohol-positive" history (APH).

4. In forensic autopsies only: Presence of alcohol in the body (usually heart blood).

An alcohol-related death (ARD) was diagnosed if, in our opinion, after analyses of all available records, alcohol consumption was deemed to the major, or underlying, factor in the causal nexus leading to death (2).

Statistical methods.

Significance of differences between proportions were tested by chi-square test for four-fold tables with one degree of freedom and with Yate's correction.

RESULTS

A total of 301 deaths occurred during the follow-up (Table I). The death rate was thus 2.9% for the whole follow-up period; 172 of these deaths occurred in those who participated in the screening, i.e. a death rate of 2.2%; 129 in the non-participants, i.e. a death rate of 4.9% ($p < 0.001$). Alcohol-related death (ARD) constituted the major mortality category, 100 out of the 301 deaths (33.2%). ARD:s were significantly more frequent among the non-participants, 57 out of 129 deaths (44.2%) than among the participants, 43 out of 172 deaths (25.0%) ($p < 0.001$), table I.

CAUSES OF DEATH IN MIDDLE-AGED MALES 4.5 years follow-up			
CAUSE OF DEATH	P (n=7725)	NP (n=2628)	TOTAL (n=10353)
CANCER	52	23	75
CARDIOVASCULAR	51	26	77
ALCOHOL-RELATED	43	57	100
MISCELLANEOUS	25	19	44
UNKNOWN	1	4	5
TOTAL	172	129	301

Table I. Causes of death in middle-aged males in the Malmö Preventive Programme, during a mean of 4.5 years follow-up after a screening at 46-48 years of age (Follow-up: 1975-1981).
P=Participants NP=Non-Participants

The death rate in ARD in the non-participants for the whole follow-up period was 27.7 per mille and in the participants 5.7 per mille ($p < 0.001$), Table II. For cancer deaths, the death rate was 8.0 vs 6.7 permille (a non-significant difference), for cardiovascular deaths 9.9 vs 6.6 permille (not significant). The mortality in participants and non-participants in relation to age is shown in fig. 1.

DEATH RATES IN PARTICIPANTS(P) VS NON-PARTICIPANTS(NP)		
CAUSE OF DEATH	P(‰)	NP(‰)
CANCER	6.7	8.7
CARDIOVASCULAR	6.6	9.9
ALCOHOL-RELATED	5.7	27.7
MISCELLANEOUS	3.1	7.2
TOTAL	22.3	49.1

Table II. Comparison of death rates (in per mille) for participants and non-participants, in relation to cause of death in middle-aged males (follow-up time, etc, see table I!)

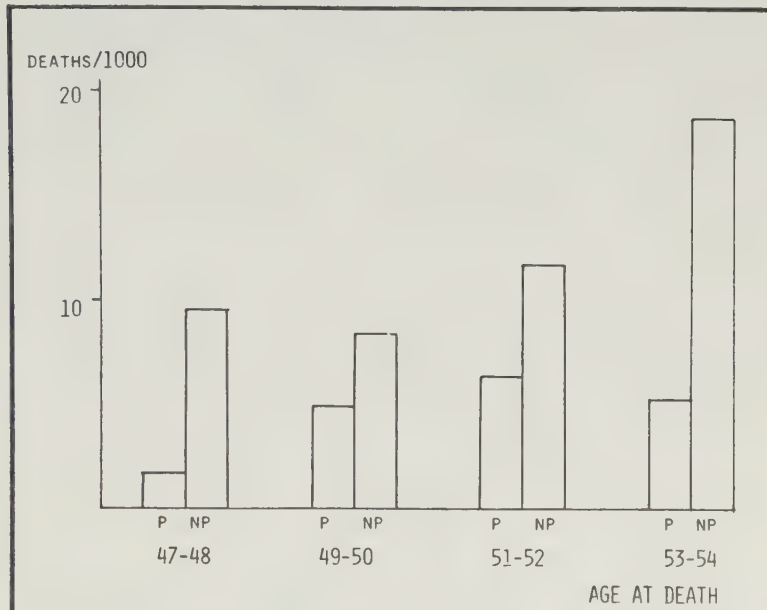


Fig. 1. The mortality in participants and non-participants in relation to age at death.

	AUTOPSY GROUP						NO AUTOPSY			TOTAL		
	IN HOSPITAL			FORENSIC								
		ARD	APH		ARD	APH		ARD	APH		ARD	APH
PARTICIPANTS	70	7	18	78	34	41	24	2	4	172	43	63
NON-PARTICIPANTS	40	10	19	76	46	53	13	1	1	129	57	73
TOTAL	110	17	37	154	80	94	37	3	5	301	100	136

TABLE III. Summary of autopsy findings and rates in whole material and in relation to alcohol history, in-hospital or forensic autopsy category, and participation/non-participation in screening.

Table III summarises the autopsy findings and rates in the whole material and in relation to autopsy category (in-hospital or forensic) and participation/non-participation groups. The autopsy rate was high, 87.7%. The highest proportion of ARD was among the non-participants autopsied at the Department of Forensic Medicine (60.5%), while in the participants autopsied in hospital only 10.0% were ARD:s. An alcohol-positive history (APH) was present in 61.0% of the subjects examined at the Forensic Department in comparison with 45.2% in the total sample.

Table IV shows the categories of alcohol-related deaths. The most common mode of ARD was 'intoxication', 34%, while cirrhosis of the liver accounted for 19%.

CATEGORIES OF ALCOHOL-RELATED DEATHS	
Accident	13
Suicide	12
Liver cirrhosis	19
Other organic complications	7
Pneumonia	4
Causa ignota	6
Intoxication	35
Other	4
Total	100

Table IV. Categories of alcohol-related deaths (ARD).

The blood alcohol concentrations at autopsy (heart blood, gas chromatographic analysis) are shown in figure 2, for the dead subjects included in the ARD/'intoxication' group. Mostly, the concentrations were below 2.0 per mille. Three subjects had alcohol in the urine only, and in one subject the exact figure was not known.

Table V demonstrates the mortality in relation to intervention for heavy drinking. An intervention group and a control group were selected from males with elevated levels of GGT (11,12). A reduction in the mortality occurred in the intervention group, although non-significant.

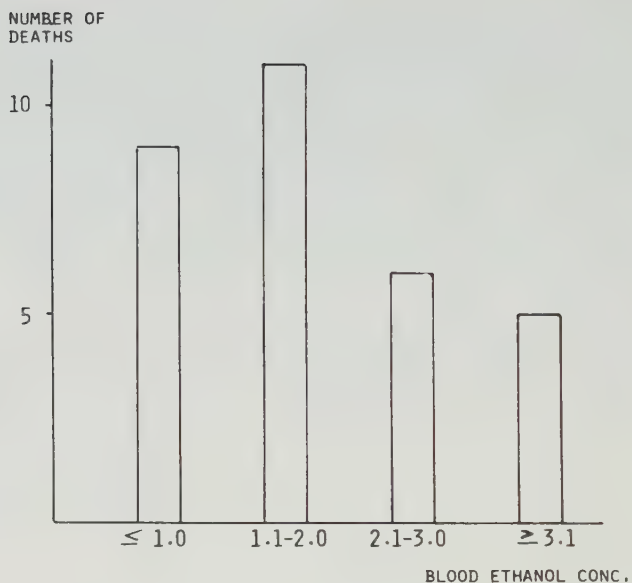


Fig. 2. Distribution of heart blood ethanol conc., in per mille, at autopsy for the group ARD/intoxications (n=35). Exact figure lacking for one subject; three subjects demonstrated alcohol in the urine only.

Cause of death	Time screening-death (months)
Intervention group (n=261)	
1. Myocardial infarction	12
2. Alcohol/barbiturate intoxication	12
3. Liver cancer	22
4. Chronic alcoholism	47
5. Pancreatic cancer	53
Control group (n=269)	
1. Bronchopneumonia	8
2. Myocardial infarction	8
3. Myocardial fibrosis	9
4. Liver cirrhosis	12
5. " "	21
6. CHD, Chronic alcoholism	21
7. Myocardial infarction	25
8. Suicide (car exhaust)	39
9. Cerebral haemorrhage, myelofibrosis	43
10. Cardiac arrhythmia, chronic alcoholism	61

Table V. Cause of death and time between screening and death within five years of follow-up of the intervention group for heavy drinking in comparison with the control group.

DISCUSSION

This study confirms that non-participation in a public health program is an important risk factor for premature death in a middle-aged urban male population. The death for non-participants during 1.5-6.5 year's follow-up was more than twice the rate in the participants. This difference to the major part dependent on the death cause category 'alcohol-related deaths'(ARD).

We do not know the reasons for non-participation in our population. Like Wilhelmsen et al. (6) we believe that the presence of chronic illness under due medical care may be one reason, but in Tibblin's study this was only the reason for a minority of the non-participants (5). Wilhelmsen et al. (6) also found that non-participants included a higher rate of alcoholics. Non-participants is probably a heterogenous group, and further studies of this group are warranted.

It has been repeatedly pointed out, among others by Bolander (13), that official death cause statistics underestimate life-style factors like alcohol and tobacco consumption. In a previous report (2) we attempted to analyse in quantitative terms the underreporting of the role of alcohol for mortality. We found that, in our population, one out of six of the deaths classified by us as alcohol-related were identified as such in the official statistics. Similar findings have also been made in a study in Vienna, byl Hackl (3).

Previous Swedish epidemiological projects (5,6,14-17) reported deaths in the "classical" manner (cancer, cardiovascular, violent, other causes), which makes comparisons of the role of alcohol difficult. It is also often difficult to establish one factor as cause of death, as many deaths have multifactorial etilogies (18). Decomposed bodies may render autopsy diagnoses uncertain in some cases. Suicidal intent is documented by the mode of death (e.g. hanging), or otherwise, by fare-well letters etc.

The most common mode of death in alcoholics in this group was sudden, unwitnessed death with a degree of alcohol intoxication demonstrated, mostly not sufficient to explain the death as a consequence of alcohol poisoning, i.e. alcohol-induced depression of the respiratory centre (19). It is postulated that complications in the abstinence phase led to the death, such as epileptic seizures or electrolyte disturbances or cardiac arrhythmias.

Non-participation presents a major obstacle to the success of a "public health strategy against alcoholism" (1). However, in the intervention project for heavy drinking in the Malmö Preventive Programme, the results are promising (8,11,12), and even a certain degree of reduction in mortality is demonstrated in this report. To further improve these results, measures should be taken to reduce the non-participation, possibly by active search/or recruitment.

The results of the intervention project thus indicate that, among the participants, alcohol-related problems may be recognized and treated in accordance with established principles for the control of risk factors, such as hypertension and hyperlipidemia.

REFERENCES

1. Lieber CS: A public health strategy against alcoholism and its complications. *Am J Med* 1978;65:722-726.
2. Petersson B, Krantz P, Kristensson H, Trell E, Sternby NH: Alcohol-related death: a major contributor to mortality in urban middle-aged men. *Lancet* 1982;2:1088-1090.
3. Hackl H: Untersuchungen zur Ermittlung der wahren Alkoholismus-Sterblichkeit. *Dtsch Med Wschr* 1980;105:1743-1747.
4. Nashold RD, Naor EM: Alcohol-related deaths in Wisconsin: The impact of alcohol on mortality. *Am J Publ Health* 1981;71:1237-1241.
5. Tibblin G: A population study of 50-year-old men. An analysis of the non-participation group. *Acta Med Scand* 1965;178:453-459.
6. Wilhelmsen L, Ljungberg S, Wedel H, Werkö L: A comparison between participants and non-participants in a primary prevention trial. *J Chron Dis* 1976;29:331-339.
7. Kristenson H, Trell E, Fex G, Hood B. Serum gamma glutamyltransferase: Statistical distribution in a middle-aged male population and evaluation of alcohol habits in individuals with elevated levels. *Prev Med* 1980;9: 108-119.
8. Kristenson H, Trell E, Hood B. Serum gamma-glutamyltransferase in screening and continuous control of heavy drinking in middle-aged men. *Am J Epidemiol* 1981;114:862-872.
9. Trell E: Community-based preventive medical department for individual risk factor assessment and intervention in an urban population. *Prev Med* 1983;12:397-402.
10. Kristenson H, Trell E: Indicators of alcohol consumption. Comparisons between a questionnaire (Mm-MAST), interviews and gamma glutamyltransferase in a health survey of middle-aged males. *Br J Addict* 1982;77:297-305.
11. Kristenson H: Studies on alcohol-related disabilities in a population study of middle-aged men. Thesis, Malmö 1982.
12. Kristenson H, Öhlin H, Hultén-Nosslin M-B, Trell E, Hood B: Identification and intervention of heavy drinking in middle-aged men: Results and follow-up of 24-60 months of long-term study with randomized controls. *Alcoholis Alcoholism: Clin Exp Res* 1983;7:203-209.

13. Bolander AM: Mortality statistics in Sweden and its neighbouring countries. In: Skandia International Symposia: Medical aspects of mortality statistics. Almqvist & Wiksell International, Stockholm 1981, pp 236-255.
14. Tibblin G, Welin L, Larsson B, Ljungberg IL, Svärdsudd K: The influence of repeated health examinations on mortality in a prospective cohort study, with a comment on the autopsy frequency. The study of men born in 1913. Scand J Soc Med 1982;10:27-32.
15. Hedstrand H: Studies in preventive medicine with particular reference to detection and treatment of risk factors for cardiovascular disease. Thesis, Uppsala 1975.
16. Lannerstad O: Death and disease in middle-aged men (in Swedish). Thesis, Studentlitteratur, Lund 1978.
17. Böttiger LE, Carlson LA: Risk factors for death for males and females. Acta Med Scand 1982;211:437-442.
18. Leiss J: Die Todesursache unter individual-patologischen Gesichtspunkten. Dtsch Med Wschr 1982;107:1069-1072.
19. Poikolainen K: Alcohol poisoning mortality in four Nordic countries. The Finnish Foundation for Alcohol Studies, Helsinki 1977.

VI

RISK FACTORS FOR PREMATURE DEATH IN MIDDLE-AGED MEN

PETERSSON, B
TRELL, E
HENNINGSEN, NC
HOOD, B

SECTION OF PREVENTIVE MEDICINE, DEPARTMENT OF INTERNAL MEDICINE,
UNIVERSITY OF LUND, MALMÖ GENERAL HOSPITAL, S 21401 MALMÖ, SWEDEN

THIS STUDY WAS SUPPORTED BY THE SWEDISH COUNCIL FOR PLANNING AND CO-
ORDINATION OF RESEARCH AND AFA (ARBETSMARKNADENS FÖRSÄKRINGSAKTIEBOLAG)

INTRODUCTION

An increased confidence has been expressed in recent years, that "the second epidemiological revolution has provided the scientific weapons for the conquest of leading non-infectious diseases through preventive measures" (1). Risk factors constitute one of the most important tools in this arsenal, as starting points and instruments for the corresponding general or individual preventive actions. However, the risk factor strategies and their results have so far mainly been confined to the cardiovascular disease field (2). In modern Western societies there exist other major forms of ill-health and death, which are of equal importance and in which there is evidence of analogous etiological connections and mechanisms, and which should therefore call for the same type of approach. The most prominent of these are the alcohol-related (3,4) and neoplastic (4,5) diseases. We have therefore aimed at analysing the full range of premature mortality and associated risk factors in the same uniform cohort of middle-aged males participating in the preventive medical population programme in Malmö, and believe that in particular the findings on alcohol-related and cancer deaths in comparison with the cardiovascular death category offer some new and complementary illumination of this field.

MATERIAL AND METHODS

Population

The Malmö Preventive Programme is an ongoing multiphasic screening and intervention population investigation directed against the current major internal medical diseases and disabilities in industrialized Western communities, such as coronary heart disease, hypertension, cancer, diabetes mellitus and smoking- and alcohol-related health problems (6). For the present study, the seven birth-year cohorts of male Malmö residents born in 1926-1932 were included. These males were between 46-48 years old at screening, which took place between the years 1975 and 1979. The cohorts in total comprised 10,353 men, of which 7,935 participated in the screening (participation rate 76.7%). The present study is restricted to the participants. The non-participants have been analysed elsewhere (4).

Screening investigation

The screening procedure has been described previously (6-7). The question-

naire included among 260 questions nine for attitude to alcohol (the Mm-MAST (8,9)), one for alcohol abstention (10) and several questions for smoking habits (11).

All laboratory analyses were performed at the Department of Clinical Chemistry, Malmö General Hospital (6-7, 12,13). Serum gamma-glutamyltransferase (GGT) was analysed according to the recommendations of the Scandinavian Enzyme Committee (14). Also all other laboratory analyses were performed according to standard methods. Serum concentrations of sodium, potassium and calcium were determined by flame photometry; triglyceride, cholesterol, urate and glucose were measured enzymatically and creatinine was determined with Jaffe's alkaline picrate method (12).

An oral glucose tolerance test was also performed (15), and a relative weight index (A/I-weight; actual/ideal weight) was calculated from the tables of Lindberg et al. (15,16). Systolic and diastolic blood pressures at 0 and 10 min, standing and recumbent, were recorded by standard methods (17).

Mortality

The mortality in the participants was followed from the day after the screening until the end of 1982. The longest follow-up time, for males born in 1926 and examined in 1975, was 8 years, and the shortest, for males born in 1932 and examined in 1979, 3.5 years. The follow-up procedure has been described previously (3,4,7-10). The completeness of the follow-up was checked by mid-81 in a nationwide matching. By then, of the 10,353 originally invited subjects, 65 (0.6%) could not be reliably classified as still living or dead. Of these, 47 had emigrated to other countries. This matching was performed using the Swedish 10-digit personal identification numbers.

During the follow-up 218 subjects died (Table I). Necropsy was performed in 181 cases (83%), about half of which (n=80) were performed by the Department of Pathology, and the other half (n=101) at the Department of Forensic Medicine.

The three major causes of death (Table I) were cancer (61/218), alcohol-related deaths (55/218) and coronary heart disease (CHD) (50/218).

The alcohol-related death causes were established according to previously

TABLE I

CANCER	61	The major mortality groups
CARDIOVASCULAR DISEASE		
CHD	50	
OTHERS	16	
ALCOHOL-RELATED DEATH	55	
MISCELLANEOUS	32	
UNKNOWN	4	
TOTAL	218	

described definitions (3,4). In the so formed category of alcohol-related death (ARD), alcohol was indicated as the sole or major underlying cause of death. This classification included the following subgroups:

1. Accidents in an alcohol-intoxicated state.
2. Organic complications to alcoholism in an alcoholic, such as cirrhosis of the liver, pancreatitis, cardiomyopathy.
3. Suicide in an alcoholic.
4. Pneumonia in an alcoholic.
5. Cause unknown in an alcoholic.
6. Intoxications, including sudden deaths in alcoholics; mostly found dead, all with alcohol in the blood, urine or tissues demonstrable at autopsy; and with no other specific cause of death, e.g. cancer, haemorrhage or myocardial infarction.
7. Others (e.g. death in delirium tremens).

Intervention

A continuing intervention program has been in operation throughout the follow-up period in corresponding out-patient clinics of the Department of Preventive Medicine (6). These services include the following conditions and cut-off levels of two consecutive measurements for intervention: Recumbent blood pressure after 10 min rest 170/105 mm Hg (160-170/95-105 mm Hg were checked annually at the Department of Preventive Medicine); serum cholesterol 7.70 mmol/l; serum triglyceride 2.20 mmol/l; GGT 1.4 μ kat/l (randomized 1:1 in treatment and control groups) and blood glucose at 120 min in oral glucose tolerance test 7.0 mmol/l (15). Other abnormal findings in the screening were also intervened upon, if indicated. More-

over, anti-smoking advice was given in subgroups (18-20), as well as dietary advice to reduce weight (21).

Further details of the results of the intervention on the alcohol-related disabilities have been reported previously (7,17,22).

Statistical methods

For each dead subject, two living controls were selected from the total population of participants and matched for screening date and age (usually $\pm$ two months). The statistical calculations were performed by comparing the entire group ($n=218$) and the various subgroups of the deceased subjects with the matched samples of still living controls ($n=436$) or the whole original screening population ($n=7935$).

The p -values for single risk factors were assessed by two-tailed Fisher's permutation test (23). The comparisons with respect to one risk factor (main or foreground variable) when a second one (background variable) was eliminated, were performed by Mantel's test (23,24). However, instead of a chi-square approximation a more accurate method was used based on the Edgeworth expansion (24). The probabilities for alcohol-related death, death due to coronary heart disease and deaths due to cancer were estimated as functions of single risk factors under order restriction (25) and as functions of several factors by use of logistic model. Estimation under order restriction was also applied on the probabilities obtained by logistic model (by considering the logistic model probability as a new variable).

It turned out that the distributions of some of the variables were so flat that a transformation of the original scales to interval scales was necessary in order to achieve satisfactory approximations of the p values.

RESULTS

GGT was the single screening variable most strongly correlated to total premature mortality in the middle-aged males ($p < 0.0001$), Table II.

For the subgroups of death, a strong positive correlation to alcohol-related death (ARD) was found for GGT ($p < 0.0001$), and a weaker for CHD deaths ($p=0.034$), but there was no association between GGT and deaths in cancer.

TABLE II

VARIABLE	UNIT	ALL-CAUSE n = 218	CANCER n = 61	CHD n = 50	ARD n = 55
GGT	$\mu\text{kat/l}$	≤ 0.0001	NS	0.034	≤ 0.0001
ALCOHOL ABSTENTION	+/-	NS	NS	NS	NS
Mm-MAST SCORE	0-4	0.016	NS	NS	≤ 0.0001
SMOKING CATEGORY	0-3	0.0002	NS	0.0062	NS
SERUM CHOLESTEROL	mmol/l	NS	0.056(-)	0.00014	0.0046(-)
SERUM TRIGLYCERIDE	mmol/l	0.022	NS	0.00013	NS
SYSTOLIC BLOOD PRESSURE	mm Hg	0.0013	NS	0.000012	NS
DIASTOLIC BLOOD PRESSURE	mm Hg	NS	NS	0.0021	NS
RELATIVE WEIGHT	INDEX	NS	NS	NS	NS
SERUM URATE	$\mu\text{mol/l}$	NS	0.023	NS	NS
SERUM CREATININE	mmol/l	0.029(-)	NS	NS	$\leq 0.0001(-)$

Results of univariate risk factor comparison between different mortality groups and matched control group by Fisher's permutation test.

(-) = inverse correlation NS = not significant

There was a weakly positive correlation of Mm-MAST score to total mortality ($p=0.016$). For the subgroups, this association was wholly confined to the alcohol-related deaths ($p\leq 0.0001$).

Smoking was strongly correlated to total mortality ($p=0.00021$), but for the subgroups this only persisted in the CHD death category ($p=0.0062$), and not in ARD or the cancer deaths ($p=0.072$).

Serum cholesterol was not associated with total mortality, but distinctly different trends in the different death cause groups made up for this non-association. Thus, there was a strong positive correlation to CHD deaths ($p=0.0014$), a strong inverse correlation to ARD ($p=0.0046$), and also significant inverse correlation to deaths in cancer (in comparison with control group $p=0.056$; in comparison with whole screening sample $p=0.031$).

Serum triglyceride, systolic blood pressure and diastolic blood pressure correlated to CHD deaths, but to none of the other causes of death. There were no associations for relative weight (A/I weight), neither to all-cause mortality nor to any of the major causes of death.

A positive correlation was present between serum urate and cancer ($p=0.023$ in comparison with matched control group), but there were no associations

to CHD or to alcohol-related deaths. Serum creatinine was strongly inversely correlated to ARD ($p < 0.0001$), and this gave a statistically significant inverse correlation also to total mortality ($p = 0.029$).

Table III shows an analysis by Mantel's test for single variables when the influence of another variable was eliminated.

TABLE III

DEATH CATEGORY	MAIN VARIABLE	BACKGROUND VARIABLE	TWO-SIDED p - VALUE
ARD	GGT	Mm-MAST SCORE	0.00047
	GGT	CHOLESTEROL	< 0.0001
	GGT	CREATININE	< 0.0001
	Mm-MAST SCORE	GGT	< 0.0001
CHD	GGT	CHOLESTEROL	0.1014 NS
	GGT	SYSTOLIC BP	0.0754 NS
	CHOLESTEROL	TRIGLYCERIDE	0.0056
	TRIGLYCERIDE	CHOLESTEROL	0.0024
	SYSTOLIC BP	DIASTOLIC BP	0.0013
	DIASTOLIC BP	SYSTOLIC BP	0.3 NS

Mantel's test comparison. BP = Blood pressure.

GGT and Mm-MAST were both of independent importance for the end-point ARD. In the group CHD death, there was no longer any association to GGT when either systolic blood pressure or serum cholesterol were taken into account. Both serum cholesterol and serum triglyceride were, independently of each other, statistically correlated to CHD. However, diastolic blood pressure was no longer correlated to CHD death when systolic blood pressure was the foreground variable.

The probability of ARD as a function of the three risk factor variables GGT, Mm-MAST score and serum creatinine is shown in Figure 1 a. The same is shown for CHD deaths as a function of the variables serum cholesterol, triglyceride and systolic blood pressure in Figure 2 a, and of smoking in Figure 2 b.

ALCOHOL-RELATED DEATH

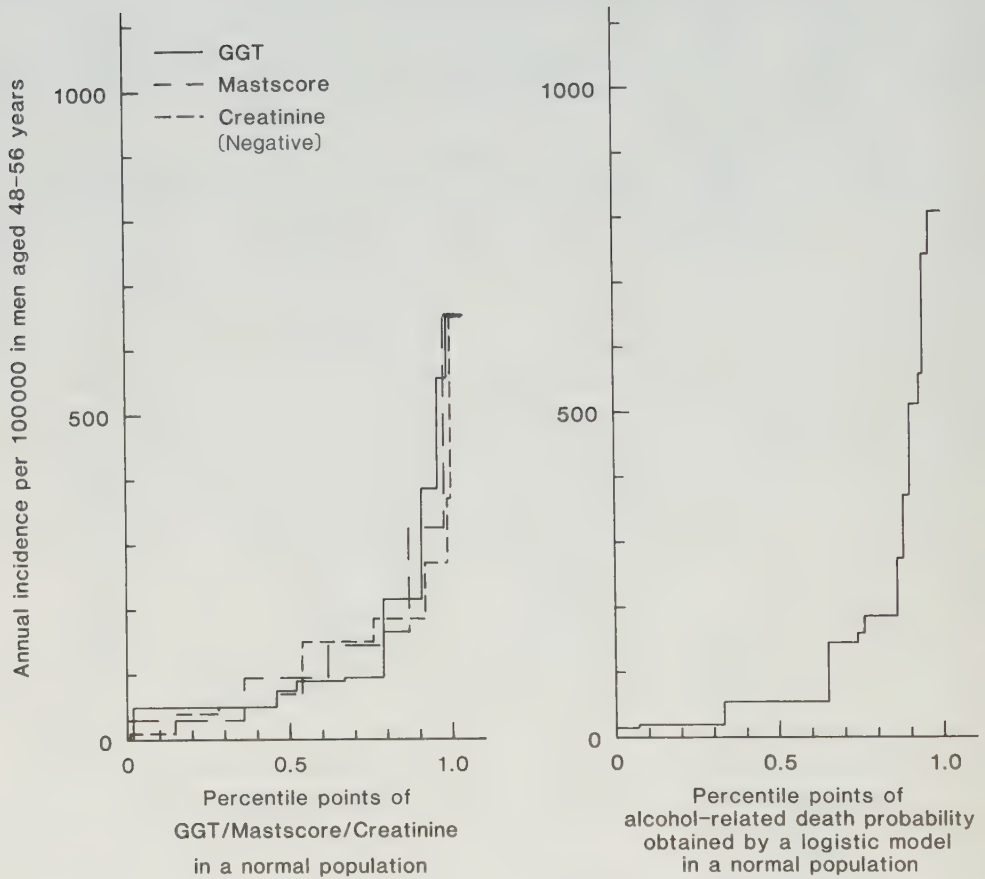


FIGURE 1 a-b. RISK FACTOR FUNCTIONS IN THE ARD GROUP.

A logistic model for the combined risk due to these groups of variables is shown in Figure 1 b for ARD and in figure 2 c for CHD. In the former category, the combination gave a moderately improved predictive power in comparison with each of the single variables, while in the CHD deaths a more pronounced improvement of the discrimination both in the lower and higher range of the respective curves was seen.

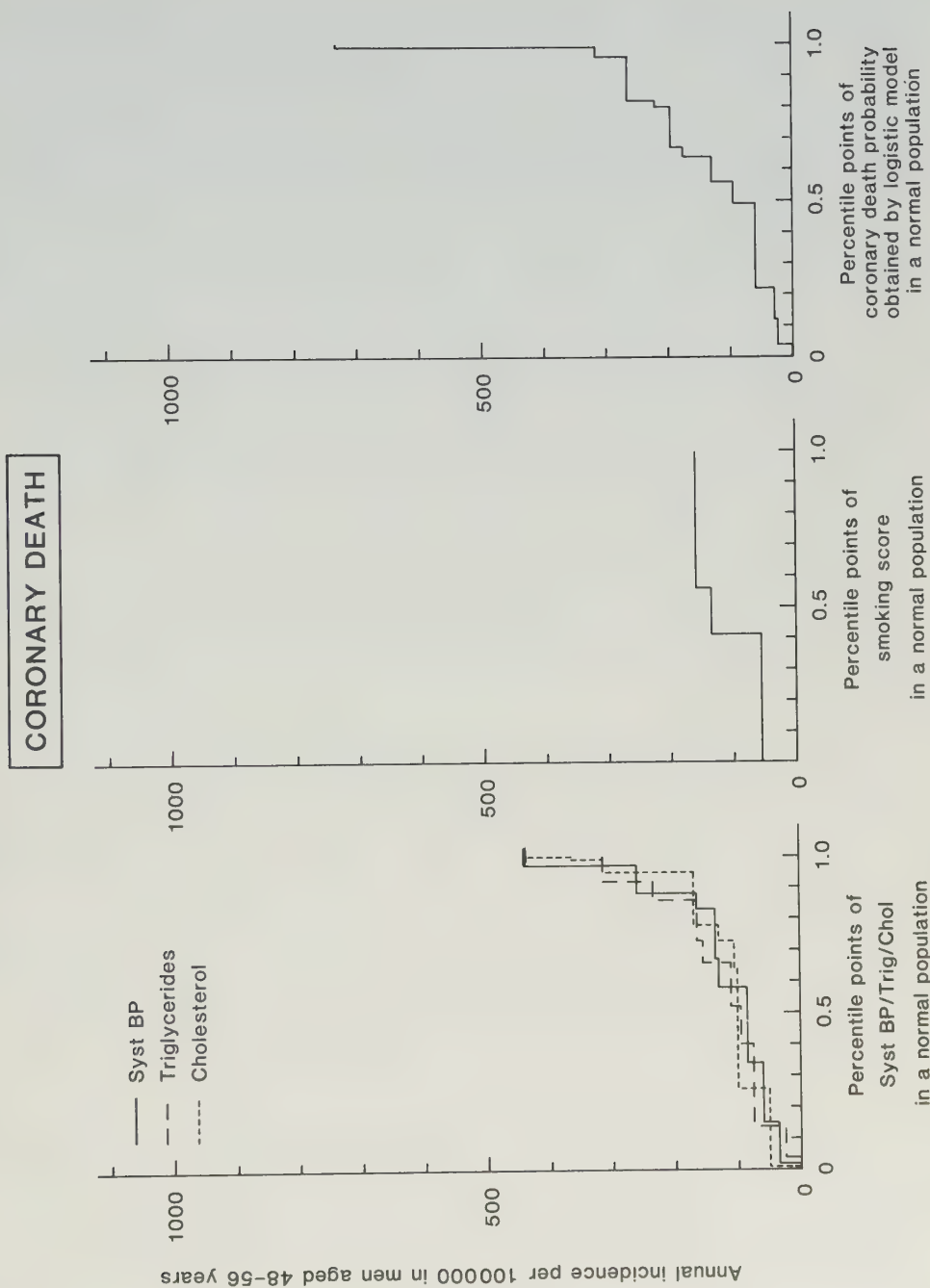


FIGURE 2 a-c. RISK FACTOR FUNCTIONS IN THE CHD MORTALITY GROUP

DISCUSSION

It is almost a truism, that the public health services ought to be organized according to the needs in the population to which they are directed. This has been the background and aim of the epidemiologically founded preventive strategies and methodologies which have been instituted predominantly against the cardiovascular diseases in the developed countries during the last few decades. Risk factors have served as important tools in this campaign. However, the spectrum of potentially avoidable major non-infectious diseases in Western societies, which "are capable of being prevented by means that have not yet been fully implemented" (2), is larger than the cardiovascular conditions, and one prerequisite for such an implementation must be a similar characterization of the structure and determinants of the actual ill-health in total age- and sex-matched as well as otherwise standardized representative population samples.

The Malmö Preventive Programme essentially covers the group of middle-aged urban males, which form the core of the productive segments of industrialized societies and to which also the bulk of previous scientific research and knowledge of risk factors and corresponding prevention has been related. We found that in our population, malignant and alcohol-related diseases constituted at least equally large groups as the cardiovascular disorders of the total premature death that occurred, still within middle age, in these cohorts. Furthermore, each of these three major categories of fatal illness was associated with a distinct and differential risk factor pattern. Possibly, these factors could then be applied, singly as well as in various combinations, both as indicators of the respective mortality and as potential signals and instruments for directed preventive measures in analogy with previously well established and tested methods for the regulation of blood pressure, serum lipids etc.

These findings were most prominent in the alcohol-related death group. Attempts at early indication and prevention of alcohol-related disabilities have therefore been in operation in the Malmö Preventive Programme since 1975, predominantly utilizing GGT as tracing, control and biochemical feed-back instrument (7,17,22). However, this approach meets two serious problems already in the identification; the non-participants and the falsely negative test results. Methods for approaching the non-participants

are therefore warranted while the false negative (as well as the false positive) group can be reduced by a more sophisticated use of the test battery (Table III, Figure 1b).

Still, when considering the results of the present risk factor assessment of the most serious diseases that occurred during the observation period in the study population, it is important to note that this was constituted by the attenders to the original screening investigation; i.e. about 75% of the whole cohorts of male Malmö residents of the same age. In these responders there is a pronounced underrepresentation of advanced alcohol-related disease in comparison with the non-participants (3,4). This makes it even more remarkable that the alcohol-related mortality was so frequent and that GGT was the single variable which correlated strongest, not only to this group but to the all-cause mortality (Table II).

However, when the major causes of death; cancer, CHD deaths and ARD, were analysed separately, it was found that GGT only was associated with the latter (Table II). There was no association to cancer deaths for GGT, which is interesting since GGT was early introduced as a test for liver involvement in malignancy (26).

The short questionnaire for alcohol habits, the Mm-MAST, which reflects the consumption habits rather than the degree of individual biological complication (9,12), was interestingly enough almost as strongly and also independently correlated with ARD as GGT. This indicates that the Mm-MAST can be utilized for the early tracing of alcohol-related disabilities. However, the problem of this method is the high rate of false positives of Mm-MAST for this end-point. About 30% of our screening population answer in the affirmative to two or more of the Mm-MAST questions, which we have applied as the screening cut-off point of the test (8-10). This gives a high yield of cases which must be subjected to further interrogation and investigation if the questionnaire is used as a single test; and it is also hard to apply a questionnaire as therapeutical feed-back and control instrument in ensuing prevention of alcohol-related disabilities (9). In conjunction with an internal medical screening and intervention program, Mm-MAST may therefore most adequately be utilized in combination with GGT and other indicators.

The strong inverse relation between serum creatinine and ARD would seem to

be of particular interest in this respect. Firstly, it confirms similar observations in two previous studies (27,28). As a likely mechanism, alcohol-induced diuresis was discussed in the first of these (27), and that a renal mechanism is involved was also suggested in the other (28). An alternative explanation is that alcoholics have low levels of androgens due to a noxious influence of ethanol on the testis (29), which, in turn, would augment the rate of creatinine synthesis in the liver. Muscle wasting, which often occurs in advanced stages of alcoholism, may also have a role for the observed creatinine lowering.

Secondly, the inverse creatinine relationship can be utilized together with other indicators like GGT and Mm-MAST in multivariate and multiple logistic risk factor functions (Fig. 1 b). Finally, it appears that serum creatinine tends to be lowered throughout the various stages of the alcohol-related disease course (12) and thus would seem to represent a continuous process, whereas many classical alcohol indicators, like blood pressure (17,30-33), serum urate (34-35) and triglyceride (36) seem to be more confined to the initial health disturbances (12) but fail as risk indicators of alcohol-related mortality (Table II).

The explanation for the statistically certified absence of the latter associations (which did occur, however, in previous health screening studies of the same population (12)) relative to the present end-point is probably that early and advanced stages of alcohol-related disorders are in different metabolic and nutritional situations. Thus, for serum urate, low levels have been reported in liver cirrhosis (37). The strong negative association of serum cholesterol and fatal alcohol-related disease in our study also supports this concept, as there has otherwise been reported a positive correlation between serum cholesterol and ethanol consumption (38), or no association at all (39,40).

Drugs are known to cause elevations of GGT, most notably barbiturates and phenantoin (41). Intake of these drugs, and of tranquilizers and analgesics is not uncommon in a population of alcoholics, and this may have contributed to the magnitude of the risk factor impact of GGT in this study. No correction has been made for this, as the role of said factors are difficult to assess in the single subject, and because the drug intake may have been a sign of the underlying condition determining the prognosis.

The mechanism for the elevation of GGT with alcohol is probably enzyme induction. It is sometimes attributed to liver cell damage. There is a rise of GGT both in the liver and in the serum with alcohol consumption (42), suggesting enzyme induction as the mechanism. It is not clear, however, why GGT enters the blood, and in case of the alkaline phosphatases, an increase is not found very frequently in serum although they are also increased in the liver with alcohol consumption (42).

It is rare to find a test which is disease specific, and GGT is no exception to this rule. Scepticism has also been forwarded against the use of GGT in the tracing of high alcohol consumers (43). However, as GGT predominantly relates to alcohol-induced health disturbances (where it hitherto seems to be superior to any other proposed tests, e.g. other liver enzymes (44), serum urate, serum ferritin (45), mean corpuscular volume (46-47), serum glutamate dehydrogenase (48), the ratio between alpha-amino-n-butyric acid and leucine (49) and others), its judicious use in a well controlled somatic health investigation situation rather ought to be encouraged, but its properties further studied.

A public health approach to alcohol-related disorders by aid of GGT and other instruments has thus been in operation in Malmö since 1975. Similar ideas have also been advocated by Lieber (50) and others. In conclusion, the findings in the present study lends support to the feasibility of identifying significant risk factors and including corresponding screening, control and biochemical feed-back methods for imminent serious alcohol-related disorders in still apparently healthy middle-aged men. Alcohol-related health problems may be included among the current leading non-infectious epidemics in both developed and developing (51) countries which are amenable to a similar type of conquest as the cardiovascular conditions, and where in comparison with the curative hospital services "the opportunities for improving health by the prevention of disease are at least as great and possibly even greater" (2).

Although several studies have focused upon risk factors for CHD, especially in middle-aged males (52-54), the role of lipids for this group of disorders is still controversial as far as the independent role of triglyceride is concerned (54,55). In the present investigation, both serum cholesterol and triglyceride were strongly significant risk factors, and contributed independently to the risk (Table III, Figure 2). Furthermore, the systolic

as well as the diastolic blood pressure were significantly associated with CHD death (Table II), but in the multivariate analysis the independent role of diastolic blood pressure disappeared (Table III). This is in accordance with the findings in the Framingham study (56). In general, all our results regarding the CHD group corresponded well with earlier studies. This supports that the other findings were genuine and relevant, too.

Perhaps the most interesting of these are the observations on the neoplastic death group. The magnitude of this premature mortality cause in the middle-aged males complies with available statistics, demonstrating that malignant neoplasms constitute an equally important death category as the cardiovascular diseases already in middle age. Sir Richard Doll recently concluded that also in cancer, "any major advance now requires an attack in middle age", and that "our two main enemies, cancer and ischemic heart disease are both essentially avoidable" by analogous measures which "mostly require changes in personal behaviour and the factors that influence it" (2). This is still in the far, but the possibility of eventually applying a similar risk factor strategy in the cancer field may be supported by the positive correlation of serum urate and negative correlation of serum cholesterol with the neoplastic deaths in the present study (Table II). Both these associations have been discussed more in detail separately (13,57). They are not as strong as the identified risk factors in the other mortality groups, but may be amplified by analyses in larger samples of cancer of different kinds, inclusion of other variables and further classification of underlying patterns, e.g. lipoprotein types (57).

REFERENCES

- 1 Jonas S, Arnold CB. The place of prevention in medical education: past, present, and future. Introduction. *Prev Med* 1981;10:661-2.
- 2 Doll R. Prospects for prevention. *Br Med J* 1983;i:445-53.
- 3 Peterson B, et al. Alcohol consumption and premature death in middle-aged men. *Br Med J* 1980;280:1403-6.
- 4 Petersson B, Krantz P, Kristenson H, Trell E, Sternby NH. Alcohol-related death: a major contributor to mortality in urban middle-aged men. *Lancet* 1982;ii:1088-90.
- 5 Fox AJ, et al. The role of epidemiology in cancer control. Report on a WHO meeting, Lyon 2-4 November 1982. WHO, ICP/CAN 015, 1983.
- 6 Trell E. Community-based preventive medical department for individual risk factor assessment and intervention in an urban population. *Prev Med* 1983;12:397-402.
- 7 Kristenson H, Trell E, Hood B. Serum gamma-glutamyl transferase in screening and continuous control of heavy drinking in middle-aged men. *Amer J Epidemiol* 1981;114:862-72.
- 8 Kristenson H, Trell E. Indicators of alcohol consumption. Comparisons between a questionnaire (Mm-MAST), interviews and serum-gamma-glutamyltransferase (GGT) in a health survey of middle-aged males. *Br J Addict* 1982;77:297-305.
- 9 Petersson B, Trell E, Kristenson H. Comparison of γ -glutamyltransferase and questionnaire test as alcohol indicators in different risk groups. *Drug Alcohol Depend* 1983;11:279-86.
- 10 Petersson B, Trell E, Kristenson H. Alcohol abstention and premature mortality in middle-aged men. *Br Med J* 1982;ii:1457-9.
- 11 Janzon L, Lindell SE, Trell E. Smoking and disease. Attitudes and knowledge in middle-aged men. *Scand J Soc Med* 1981;9:127-33.
- 12 Petersson B, et al. Comparison of gamma-glutamyltransferase and other health screening tests in average middle-aged males, heavy drinkers and alcohol non-users. *Scand J Clin Lab Invest* 1983;43:141-9.
- 13 Petersson B, Trell E. Raised serum urate concentration as risk factor for premature mortality in middle-aged men: relation to death from cancer. *Br Med J* 1983;ii:7-9.

- 14 Scandinavian enzyme committee. Recommended methods for the determination of gamma-glutamyltransferase in blood. *Scand J Clin Lab Invest* 1976; 36:119-25.
- 15 Janzon L, Berntorp K, Hanson M, Lindell SE, Trell E. Glucose tolerance and smoking: a population study of oral and intravenous glucose tolerance tests in middle-aged men. *Diabetologia* 1983;25:86-8.
- 16 Lindberg W, Natvig H, Rygh A, Svendsen K. Höyde og vektsundersökelse hos voksne menn og kvinner. *Tidskr Norsk Laegeforen* 1956;76:231-71.
- 17 Henningsen NC, Janzon L, Trell E. Influence of carboxyhemoglobin, gamma-glutamyl-transferase, body weight, and heart rate on blood pressure in middle-aged men. *Hypertension* 1983;5:560-3.
- 18 Janzon L, Lindell SE, Trell E, Larne P. Smoking habits and carboxyhemoglobin. *J Epidemiol Community Health* 1981;35:271-3.
- 19 Trell E, et al. Rauchgewohnheiten, Kohlenmonoxydhämoglobin und Lungenkrankheiten. *Prax Klin Pneumol* 1983;37:561-4.
- 20 Trell E, Trell L, Janzon L, Laurell P, Korsgaard R. Verbesserung der Motivation zur Rauchentwöhnung bei Individuen mit Genetischen Risikofaktoren für Lungenkrebsentwicklung. *Prax Klin Pneumol* 1983;37:1020-4.
- 21 Larsson L, Trell E. (Nutritionist in Preventive Medicine. Some experiences from the Department of Preventive Medicine in Malmö.) *Socialmedicinsk Tidskr* 1983;60:325-6.
- 22 Kristenson H, Öhlin H, Hulthén-Nosslin MB, Trell E, Hood B. Identification and intervention of heavy drinking in middle-aged men: results and follow-up of 24-60 months of long-term study with randomized controls. *Alcoholism: Clin Exp Res* 1983;7:203-9.
- 23 Mantel N. Chi-square tests with one degree of freedom: Extensions of the Mantel-Haenszel procedure. *J Am Stat Assoc* 1963;58:690-700.
- 24 Cramér H. Mathematical methods of statistics. Princeton University Press 1946.
- 25 Barlow RE, Bartholomew DJ, Bremner JM, Brunk HD. Statistical inference under order restrictions. New York: Wiley, 1972.
- 26 Aronsen KF, Nosslin B, Pihl B. The value of gamma-glutamyl transpeptidase as a screen test for liver tumor. *Acta Chir Scand* 1970;136:17-22.

- 27 Chan-Yeung M, et al. The effects of age, smoking and alcohol on routine laboratory tests. *Am J Clin Pathol* 1981;75:320-6.
- 28 Gill et al. Acute biochemical responses to moderate beer drinking. *Br Med J* 1982;ii:1770-3.
- 29 Wälimäki M, Ylikahri R. Alcohol and sex hormones. *Scand J Clin Lab Invest* 1981;49:99-105.
- 30 Klatsky AR, Friedman GD, Siegelau AB, Gérard MJ. Alcohol consumption and blood pressure. Kaiser-Permanente multiphasic health examination data. *N Engl J Med* 1977;276:1194-1200.
- 31 Larbi EB, Cooper RS, Stamler J. Alcohol and hypertension. *Arch Int Med* 1983; 143:28-9.
- 32 Henningsen NC, et al. Hypertension, levels of serum gamma-glutamyltranspeptidase and degree of blood pressure control in middle-aged males. *Acta Med Scand* 1980;207:245-51.
- 33 Mathews JD. Alcohol use, hypertension and coronary heart disease. *Clin Sci Mol Med* 1976;51:661-3.
- 34 Lieber CS, Jones DP, Losowsky MS, Davidson CS. Interrelation of uric acid and ethanol metabolism in man. *J Clin Invest* 1962;41:1863-70.
- 35 Faller J, Fox IH. Ethanol-induced hyperuricemia. Evidence for increased urate production by activation of adenine nucleotide turnover. *N Engl J Med* 1982; 307:1598-602.
- 36 Chait A, February AW, Mancini M, Lewis B. Clinical and metabolic study of alcoholic hyperlipidemia. *Lancet* 1972;ii:62-4.
- 37 Higuchi T, Nakamura T, Uchino H. Enhanced renal clearance of uric acid in hepatic cirrhosis. *Isr J Med Sci* 1981;17:1015-8.
- 38 Grande F, Amatuzio DS. The influence of ethanol on serum cholesterol concentration. *Minnesota Med* 1960:731-5.
- 39 Belfrage P, et al. Alterations of lipid metabolism in healthy volunteers during long-term ethanol intake. *Eur J Clin Invest* 1977;7:127-31.
- 40 Castelli WP, et al. Alcohol and blood lipids. The cooperative lipoprotein phenotyping study. *Lancet* 1977;ii:153-5.

- 41 Rosalki SB, Tarlow D, Rau D. Plasma gamma glutamyltranspeptidase elevation in patients receiving enzyme-inducing drugs. *Lancet* 1971;ii:376-7.
- 42 Teschke R, Neufeind M, Nishimura N, Strohmeyer G. Hepatic gamma-glutamyl-transferase activity in alcoholic fatty liver: comparison with other liver enzymes in man and rats. *Gut* 1983;24:625-30.
- 43 Penn R, Worthington DJ. Is serum gamma-glutamyltransferase a misleading test? *Br Med J* 1983;286:531-5.
- 44 Horner F, et al. Dynamic changes of serum gamma-glutamyl transferase in chronic alcoholism. *Enzyme* 1979;24:217-23.
- 45 Kristenson H, Fex G, Trell E. Serum ferritin, gammaglutamyl-transferase and alcohol consumption in healthy middle-aged men. *Drug Alcohol Depend* 1981; 8:43-50.
- 46 Wu A, Chanarin I, Leevy AJ. Macrocytosis of chronic alcoholism. *Lancet* 1974; i:829-31.
- 47 Bagrel A, d'Houtaud A, Gueguen R, Siest G. Relation between reported alcohol consumption and certain variables in an unselected population. *Clin Chem* 1979;25:1242-6.
- 48 Van Waes L, Lieber CS. Glutamate dehydrogenase: a reliable marker of liver cell necrosis in the alcoholic. *Br Med J* 1977;ii:1508-10.
- 49 Shaw S, Stimmel B, Lieber CS. Plasma alfa-amino-n-butyric acid/leucine ratio: an empirical biochemical marker of alcoholism. *Science* 1976;194:1057-8.
- 50 Lieber CS. A public health approach for the control of the disease of alcoholism. *Alcoholism* 1982; 6: 171-7.
- 51 Edwards G. Drinking problems: putting the third world on the map. *Lancet* 1979; ii:402-6.
- 52 Dawber TR. The Framingham Study. The epidemiology of atherosclerotic disease. Cambridge, Massachusetts: Harvard University Press, 1980.
- 53 Keys A. Seven Countries. A multivariate analysis of death and coronary heart disease. Cambridge, Massachusetts: Harvard University Press, 1980.
- 54 Böttiger LE, Carlson LA. Risk factors for death for males and females. A study of the death pattern in the Stockholm Prospective Study. *Acta Med Scand* 1982;211:437-42.

- 55 Hulley SB, Rosenman RH, Bawol RD, Brand RJ. Epidemiology as a guide to clinical decisions: the association between triglyceride and coronary heart disease. *N Engl J Med* 1980;302:1383-9.
- 56 Kannel W, Gordon T, Schwartz MJ. Systolic versus diastolic blood pressure and risk of coronary heart disease: The Framingham Study. *Am J Cardiol* 1971; 27:335-46.
- 57 Petersson B, Trell E. Premature mortality in middle-aged men: serum cholesterol as risk factor. *Klin Wochenschr* 1983;63:795-801.

COMPARISON OF γ -GLUTAMYLTRANSFERASE AND QUESTIONNAIRE TEST AS ALCOHOL INDICATORS IN DIFFERENT RISK GROUPS*

BO PETERSON, ERIK TRELL and HANS KRISTENSON

Section of Preventive Medicine, Departments of Internal Medicine and Alcohol Diseases, University of Lund, Malmö General Hospital, S-214 01 Malmö and Department of Internal Medicine, Hässeholms Hospital, S-281 00 Hässeholm (Sweden)

(Received March 17th, 1983)

SUMMARY

γ -Glutamyltransferase (γ -GT) and a Malmö modification of the Michigan Alcoholism Screening Test (Mm-MAST) were compared in subsamples of a health screening population of urban middle aged males with characterized levels of alcohol consumption and in the total group of deaths 0–6 years after the screening investigation. The questionnaire was markedly superior to γ -GT in identifying the alcohol consumption in the known alcoholics but not in the other study groups. γ -GT may be indicative of alcohol related health disturbances and may be used in their early recognition and as biochemical feedback in their further treatment and control in individuals. It may therefore be of value particularly as an instrument in a programme aimed at prevention of alcohol-related health complications.

Key words: Alcohol – γ -Glutamyltransferase – MAST – Prevention – Questionnaire – Screening tests

INTRODUCTION

There is an increasing awareness in the medical community that, as expressed very accurately by Bernadt et al. [1], 'the growing prevalence of alcohol-related disorders poses major problems for medical, surgical and psychiatric services throughout the developed world.' These authors also

*This study was supported by the Swedish Council for Planning and Coordination of Research. Abbreviations: APH, alcohol-positive history; γ -GT, γ -glutamyltransferase; Mm-MAST, Malmö modification of the Michigan Alcoholism Screening Test.

noted that in response to this situation a number of rapid interview techniques for detecting alcoholism have been applied by American researchers, while in Europe and Australia the main emphasis has been placed on biometrical markers, in particular serum γ -GT. The latter methods indicate biological reactions possibly induced by alcohol rather than the exact consumption levels. Questionnaires and laboratory tests would therefore seem to refer predominantly to either of the two complementary aspects of alcohol-related problems, i.e. consumption on the one hand and the harm associated with it on the other. This is probably the reason for different conclusions regarding their efficacy and usefulness [1-4]. Also the composition of the risk group and the nature of the risk studied will influence the results. Although suggested by WHO [5], no comparative studies on this particular dilemma have been reported so far. Bernadt et al. [1] in their excellent analysis of questionnaires and laboratory tests mainly focussed on heavy drinking and alcoholism in a psychiatric high-risk group where the main risk was that of excessive alcohol intake. In this situation and in indicating the quantitative level of alcohol consumption, the results of questionnaires were markedly superior to the laboratory values. We have compared questionnaire and laboratory tests in other groups and modalities of risk and believe that the results may provide complementary information on this important medical issue.

MATERIALS AND METHODS

Preventive investigation

Details of the Malmö preventive programme have been presented elsewhere [6,7]. Total birth-year cohorts of middle-aged male Malmö residents were invited to a health screening. For the purpose of the present study, subgroups of the birth year cohorts 1926-32, examined during the years 1975-79, were included. These total cohorts comprised 10 353 men invited to the screening, of which 7725 (74.6%) participated. The subjects' age was between 46 and 48 years at screening. All screening attenders answered an extensive questionnaire comprising 260 questions. From April 1976, 9 alcohol questions (Mm-MAST, Table I) were also included [4,8]. A tenth question: 'Are you a teetotaler?' was given as well. The nine Mm-MAST questions reflect alcohol habits and attitudes and correspond to the MAST modification applied by Bernadt et al. [1,4,8]. The cut-off point for possible overconsumption was ≥ 2 'yes' answers [4,8]. Altogether, the Mm-MAST was obtained in 5410 men of the study population.

The screening procedure was followed by an intervention programme for hypertension, hyperlipidemia, impaired glucose tolerance and other risk factors detected and confirmed during screening [6,7]. One of the aims of the programme was to investigate the practicability of using the enzyme serum γ -GT for the detection and in the continuous control of alcohol-related problems [6,7]. γ -GT was analysed according to the recom-

TABLE I

TOTAL NUMBER OF YES-ANSWERS TO QUESTION OF ABSTAINING AND DIFFERENT Mm-MAST QUESTIONS IN 4350 MIDDLE-AGED MEN AT SCREENING AND GGT PERCENTILES ($\mu\text{kat/l}$) IN EACH GROUP

	Answers		GGT percentiles*		
	N	%	P 50	P 90	P 95
(A) Are you a teetotaler?	286	5.8	0.39	0.96	1.61
1. Do you take a drink before going to a party?	714	14.5	0.51	1.59	2.28
2. Do you usually drink a bottle of wine or corresponding amounts of alcohol over the week-end?	1122	22.7	0.49	1.38	2.08
3. Do you drink a couple of drinks (or beers) a day to relax?	240	4.8	0.67	2.45	4.55
4. Do you tolerate more alcohol now than you did ten years ago?	395	8.0	0.47	1.77	2.43
5. Have you difficulties not drinking more than your friends?	137	2.8	0.49	1.56	2.33
6. Do you fall asleep after moderate drinking without knowing how you got to bed?	227	4.6	0.51	1.24	1.80
7. Do you have a bad conscience after drinking?	347	7.0	0.49	1.72	2.49
8. Do you take a drink (a beer) the day after a party?	667	13.5	0.51	1.52	2.24
9. Do you try to avoid alcoholic beverage for a determined period of time e.g. a week?	805	16.3	0.49	1.49	2.36

*For the whole background population the GGT median was $0.46 \mu\text{kat/l}$ and the P 90 and P 95 $1.40 \mu\text{kat/l}$ and $1.91 \mu\text{kat/l}$, respectively.

recommendations of the Scandinavian Enzyme Committee [9]. The upper normal reference limit in our laboratory corresponds to $1.08 \mu\text{kat/l}$.

Health screening study groups

The following subgroups from the screening population were selected for the comparison of Mm-MAST and γ -GT:

(i) Heavy drinkers. Half of the individuals with screening γ -GT values in the top decentile of the distribution ($\geq 1.40 \mu\text{kat/l}$), were invited to a special outpatient clinic for investigation of alcohol-related problems. After detailed interviews of their alcohol habits, 54% of these individuals were classified as excessive drinkers ($>40 \text{ g/day}$), 22% as moderate ($20\text{--}40 \text{ g/day}$), 19% as light alcohol consumers ($<20 \text{ g/day}$) and 5% as non-users [7]. The present study includes a total consecutive sub-group of 125 of the heavy and moderate drinkers (76% of the top decentile γ -GT group) in this material [4,7].

(ii) Normal γ -GT group (γ -GT < P90). An age- and sex-matched subgroup with screening GT value below the 90th percentile of the distribution ($N = 58$) were interviewed in the same way as group (i). Forty-one (71%) were classified as light drinkers or non-users (NA); 7 (12%) as moderate; 10 (17%) as heavy alcohol consumers (A), using the same criteria as in group (i).

(iii) All participants still living in Malmö who had at least once been admitted to and registered at the Department of Alcohol Diseases (RAD) between 1968–1979 ($N = 223$).

Post-mortem material

The mortality after screening in the whole screening population was followed for the years 1975–1980 with a follow-up period of 0–6 years (mean: 3 years) [8,10]. Information on deaths was obtained from a file at the Department of Pathology, Malmö General Hospital, where all deaths in Malmö residents are registered. Deaths that occurred in subjects after moving out of town are thus not included in this analysis. For the deceased, all available sources of information were searched, e.g. screening protocols, hospital records, police protocols, autopsy reports and death certificates. Possible registration at the Department of Alcohol Diseases (RAD) was checked. If a deceased subjected was registered at this department, or if in any of the above-mentioned sources it was stated that he was known as an alcohol abuser, he was labelled as having an 'alcohol-positive history' (APH). Among all deaths ($N = 127$) which had occurred in the screening attenders 48 had an APH. γ -GT was obtained in all the cases from the post-mortem material, while Mm-MAST was obtained only in those born after 1927, altogether 82 cases.

RESULTS

Table II summarizes the results of the Mm-MAST and γ -GT comparisons in the screening study groups. Altogether 76% of the individuals with γ -GT in the top decile had heavy or moderate drinking, which thus corresponds to a predictive value of 76% of the γ -GT test. The Mm-MAST test was positive in 66% of this group, and in the whole γ -GT normal subgroup in 31%. However 94% of the cases in the γ -GT normal group in whom the interview had verified heavy or moderate alcohol consumption, and which were accordingly misclassified by the γ -GT method, had a positive Mm-MAST result. Among the known alcoholics, finally, 73% had ≥ 2 Mm-MAST answers, while the frequency of increased γ -GT in this group was 31%.

Table III compares the sensitivity, specificity, positive predictive value, negative predictive value and efficiency of γ -GT and Mm-MAST in the post-mortem material with an alcohol-positive history. The sensitivity for γ -GT of identifying the alcohol abusers within the mortality material was 0.53 and the specificity 0.85. The sensitivity for Mm-MAST was higher:

TABLE II
FREQUENCY OF POSITIVE (≥ 2 'YES' ANSWERS) AND NEGATIVE (< 2 'YES' ANSWERS) Mm-MAST RESULTS IN THE DIFFERENT SCREENING STUDY GROUPS AND IN THE WHOLE SCREENING POPULATION OF MALE PARTICIPANTS OF THE SAME AGE (BIRTH YEAR COHORT 1928).

NA, not alcohol; A, alcohol overconsumption.

γ -GT $< 1.40 \mu\text{kat/l}$, $N = 58$									
NA: $N = 41$ (76%)		A: $N = 17$ (29%)		γ -GT $\geq 1.40 \mu\text{kat/l}$ A: $N = 125$ (76%)		Known alcoholics ^a $N = 223$		All participants born in 1928, $N = 1187$	
N	%	N	%	N	%	N	%	N	%
Mm-MAST ≥ 2	2	16	94	82	66	163	73	345	29
Mm-MAST [†] < 2	39	1	6	43	34	60	27	842	71

^a31% had γ -GT $\geq 1.40 \mu\text{kat/l}$.

TABLE III

SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE, NEGATIVE PREDICTIVE VALUE AND EFFICIENCY FOR γ -GT ($\geq 1.40 \mu\text{kat/l}$), Mm-MAST (≥ 2 'YES' ANSWERS) AND A COMBINATION OF γ -GT AND Mm-MAST TO CORRECTLY IDENTIFY A GROUP OF DEAD MEN WITH AN ALCOHOL-POSITIVE HISTORY IN WHOM THESE TEST WERE OBTAINED AT SCREENING.

SENS, proportion of true positive cases in positive tests; SPEC, proportion of true negative cases in negative tests; PPV, ratio true positive tests over all positive tests; NPV, ratio true negative tests over all negative tests; EFF, proportion of true positive and true negative tests of all tests.

	γ -GT $\geq 1.40 \mu\text{kat/l}$	Mm-MAST ≥ 2	γ -GT $\geq 1.40 \mu\text{kat/l}$ and/or Mm-MAST ≥ 2
SENS	0.53	0.70	0.68
SPEC	0.85	0.69	0.68
PPV	0.68	0.47	0.55
NPV	0.76	0.85	0.78
EFF	0.73	0.70	0.68

0.70, but the specificity lower: 0.69. The positive predictive value for γ -GT was 0.68 in this sample, but for Mm-MAST only 0.47. The overall efficiency for γ -GT was in the same range as for Mm-MAST: 0.73 and 0.70. A combination of γ -GT and Mm-MAST reached sensitivity and specificity comparable with Mm-MAST alone, but the positive predictive value of 0.55 was better.

DISCUSSION

These examples illustrate various types of screening purposes, risks and end-points which are highly pertinent to the present perspective of alcohol-related disorders in Western societies, as well as to the corresponding public health strategies which have been proposed [11,12]. It is then important to consider the instruments not only as indicators of consumption. The correlation of complex biochemical responses to precise quantities of intake is often difficult, depending, e.g., on variability by age and sex, body weight and other individual factors. This is particularly true of γ -GT [2], which nonetheless is considered to be the best available biochemical method [1]. When we compared a simple questionnaire test with γ -GT in subgroups of an ordinary urban middle-aged male population, they showed about equally good predictive value in relation to excessive drinking, while the questionnaire test was superior in identifying the known alcoholics (Table I). These findings support that if screening for consumption levels is the sole objective, a questionnaire instrument is as good as or superior to, γ -GT also in a health investigation [1]. However, in the same screening population and subsamples, we have earlier demonstrated that the main value of γ -GT is that it may indicate individuals with current alcohol-related health prob-

lems and/or at risk of alcohol-related disabilities [5]; and this applies to both medical [6,7,13-16] and social disturbances [17]. This may be supported also by the finding in our health screening study groups that the efficacy of Mm-MAST was best in the group of heavy or moderate alcohol consumers without increase of γ -GT, i.e., where mainly the alcohol habits themselves were exaggerated but no biological reaction yet apparent (Table II). Furthermore, in a somatic health programme, γ -GT may then also be used as biochemical feedback and control instrument in the prevention of the alcohol-related complications which it identifies [6]. Therapeutic improvement is accompanied and reinforced by demonstrable decrease of the γ -GT value [7]. It is much more difficult to use psychological attitudes and habits of alcohol consumption in any of these respects.

In the post-mortem material, which represents the most urgent medical demands in Malmö in the corresponding age group and time period, a confirmed history of alcohol abuse was presented in 46.2% [10]. In this group of ascertained excessive drinking, Mm-MAST was somewhat more sensitive than γ -GT while γ -GT showed the best predictive value. This is markedly at variance with the findings of Bernadt et al., in the psychiatric out-patient material [1]. Yet, there is in principle no difference between their investigation and ours regarding neither the completeness or representativity of the materials nor the methods. Even if our groups are smaller, they might be better defined in terms of uniformity in age and sex as well as in representativity in relation to the whole underlying population. Probably, our findings illustrate that the methodological standards as well as the selection and the nature of the high risk-population will markedly influence the results and conclusions of the study. Our conclusion is that questionnaire tests in most situations, including health screenings, are superior to biochemical tests in identifying the alcohol consumption patterns. However, γ -GT appears to be especially helpful for the recognition of alcohol-related health risks and disabilities as well as for their individual prevention and treatment in a public health strategy directed against alcohol and its complications [11,12].

REFERENCES

- 1 M.W. Bernadt et al., *Lancet*, 1 (1982) 325.
- 2 A. Bagrel, A. d'Houtaud and R. Gueguen, *Clin. Chem.*, 25 (1979) 1242.
- 3 J.B. Whitfield, W.J. Hensley and D. Bryden, *Ann. Clin. Biochem.*, 15 (1978) 297.
- 4 H. Kristensson and E. Trell, *Br. J. Addict.*, 77 (1982) 297.
- 5 WHO Group of Investigators, in: *Alcohol-Related Disabilities*, WHO Offset Publication no. 32, World Health Organization, Geneva, 1977.
- 6 H. Kristensson et al., *Prev. Med.*, 9 (1980) 108.
- 7 H. Kristensson, E. Trell and B. Hood, *Am. J. Epidemiol.*, 114 (1981) 862.
- 8 B. Petersson, E. Trell and H. Kristensson, *Br. Med. J.*, 2 (1982) 1457.
- 9 The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology, Recommended methods for the determination of γ -glutamyltransferase in blood, *Scand. J. Clin. Lab. Invest.*, 36 (1976) 119.

- 10 B. Petersson et al., *Lancet*, 2 (1982) 1088.
- 11 C.S. Lieber, *Am. J. Med.*, 65 (1978) 722.
- 12 Anonymus, *Lancet*, 2 (1980) 1117.
- 13 B. Petersson et al., *Br. Med. J.*, 1 (1980) 1403.
- 14 E. Trell et al., *Ann. Clin. Biochem.*, 17 (1980) 134.
- 15 H. Kristensson et al., *Drug Alcohol Depend.*, 9 (1982) 325.
- 16 H. Kristensson et al., *Lancet*, 1 (1980) 1141.
- 17 H. Kristensson, J. Öhrn and B. Hood, *Prev. Med.*, 11 (1982) 403.

Alcohol abstinence and premature mortality in middle-aged men

**BO PETERSSON, ERIK TRELL,
HANS KRISTENSON**

Abstract

A series of middle-aged men were investigated for total mortality up to five years after completing a questionnaire on alcohol consumption administered during a preventive medical screening programme in Malmö, Sweden. The aim was to test the hypothesis that small amounts of alcohol are beneficial to general and cardiovascular health.

Relative mortality was increased among the men who had reported non-use of alcohol in the screening questionnaire. Most of these men, however, had chronic disease as the reason for their abstinence, or even a past history of alcoholism.

Increased mortality in non-drinkers may create a false impression of a preventive effect of any versus no daily drinking in relation to general and cardiovascular health.

Introduction

Several studies have suggested that small amounts of alcohol may be beneficial for general and cardiovascular health.¹⁻⁶ A "cardioprotective" effect of alcohol has been postulated, mediated by, for example, decreased platelet aggregation and

**Section of Preventive Medicine, Department of Internal Medicine,
University of Lund, Malmö General Hospital, S-21401 Malmö,
Sweden**

**BO PETERSSON, MD, associate researcher in preventive medicine
ERIK TRELL, MD, associate professor in preventive medicine**

**Department of Alcohol Diseases, University of Lund, Malmö
General Hospital, S-21401 Malmö, Sweden**

HANS KRISTENSON, MD, associate professor in alcohol diseases

coagulation or increased α -lipoprotein concentrations, or both.¹⁻⁶ These studies have partly been based on comparing mortality ratios in drinkers and non-drinkers, which tend to support "a small preventive effect of any versus no drinking."² As a group, however, "abstainers" may not represent people with a smooth continuum of non-drinking but be widely heterogeneous both in their past history of alcohol use and in their morbidity composition. For example, a substantial proportion of non-drinkers may have diagnosed or symptomatic illness as the main reason for their current abstinence, and some may be temporarily reformed alcoholics.

In a preventive medical screening programme in Malmö we administered a questionnaire on alcohol consumption⁷ and used biochemical markers of alcohol-related metabolic effects.⁸ We report here on the increased premature mortality among men who had stated in the questionnaire that they abstained from drinking alcohol.

Subjects and methods

Screening investigations—During 1974-9 all male residents of Malmö born in 1926, 1927, 1928, 1929, 1930, 1931, and 1932 were invited to attend for screening at the department of preventive medicine at this hospital. Subjects were divided into cohorts according to year of birth and the cohorts approached consecutively. Of all 10 353 men contacted, 7725 (74.6%) participated. Investigations included measurements of height and weight, pulse rate, blood pressure (standing and recumbent, and before and after 10 minutes' rest), and skinfold thickness; simple pulmonary function tests; electrocardiogram; and several fasting laboratory estimations, including γ -glutamyltransferase activity. All laboratory analyses were performed according to standard methods in the department of clinical chemistry.

Questionnaire on alcohol consumption—All screening attenders answered a questionnaire containing 260 questions and presented either as an ordinary form, or as preprinted punch cards in a card-collecting box,⁹ or directly by interactive computer terminals.⁹ From April 1976 nine questions on alcohol consumption (Malmö modification of brief MAST; Mm-MAST) were included.⁷ A tenth question "Are you a teetotaller?" was also included to get an approximate number of abstainers in the population. The questions on alcohol consumption were included in 90 of the questionnaires given to men born in 1927 and in all of the questionnaires used for subsequent cohorts. Altogether 5410 men answered the questions on alcohol consumption (table I).

Mortality analyses—Records of deaths among the screened population up to the end of 1980 were obtained from the department of pathology, which is notified of all deaths among Malmö residents. Stated causes of death were confirmed by reviewing clinical records, necropsy reports, and police reports; all forensic necropsy reports were reviewed by one of us. Possible registration at the department of alcohol diseases was searched for and the screening protocols reviewed. All Swedes have a 10-digit identification number, which facilitates such record linkages. In classifying mortality we used one

TABLE I—Proportions of men answering "yes" to questions on alcohol consumption, and percentiles of γ -glutamyltransferase activity in each answer group

	No (%) of men answering affirmatively*		γ -Glutamyltransferase percentiles†		
			P 50	P 90	P 95
(A) Are you a teetotaler?	286	(5.8)	0.39	0.96	1.61
(1) Do you take a drink before going to a party?	714	(14.5)	0.51	1.59	2.28
(2) Do you usually drink a bottle of wine or corresponding amount of alcohol over the weekend?	1122	(22.7)	0.49	1.38	2.08
(3) Do you drink a couple of drinks (or beers) a day to relax?	240	(4.8)	0.67	2.45	4.55
(4) Do you tolerate more alcohol now than you did 10 years ago?	395	(8.0)	0.47	1.77	2.43
(5) Have you difficulties not drinking more than your friends?	137	(2.8)	0.49	1.56	2.33
(6) Do you fall asleep after moderate drinking without knowing how you got to bed?	227	(4.6)	0.51	1.24	1.80
(7) Do you have a bad conscience after drinking?	347	(7.0)	0.49	1.72	2.49
(8) Do you take a drink (or a beer) the day after a party?	667	(13.5)	0.51	1.52	2.24
(9) Do you try to avoid alcohol for a determined period of time—for example, a week?	805	(16.3)	0.49	1.49	2.36

*Results shown for all 4350 men born in 1928-31 and 90 men born in 1927. Results for 950 men born in 1932 showed same distribution but are excluded from table.

†For whole background population median γ -glutamyltransferase activity was 0.56 μ kat/l and P 90 and P 95 1.40 and 1.91 μ kat/l, respectively.

own criteria for alcohol-related death,¹⁰ which are based on the definitions of the WHO for alcohol-related disabilities.¹¹ Hence alcohol-related death was recorded when we could reasonably infer that alcohol was the major factor. Other deaths were classified according to standard criteria.

Statistical methods—All screening results, including the results of the questionnaires, were fed into a NOVA 830 computer for later retrieval and analysis. The results of the alcohol questionnaire were grouped into seven categories, A and 0-5 (A, men reporting alcohol abstinence; 0-5, men answering yes to from none to five or more of the questions) (see table II). The total mortality and its distribution were analysed in relation to these results. Significance of differences between the various answer categories and of trend in the non-abstainers was assessed by χ^2 test. Expected answer frequencies were obtained from a series of matched controls (see below).

TABLE II—Distribution of men who died and of living controls among seven categories of reported alcohol consumption. Figures are number (%) of men

Category of alcohol consumption	Dead (n = 82)	Living (n = 155)	Observed: expected ratio
Abstinence	7 (8.5)	6 (3.9)	2.20
0	27 (32.9)	71 (45.8)	0.72
1	14 (17.1)	38 (24.5)	0.70
2	13 (15.9)	20 (12.9)	1.23 (NS)
3	13 (15.9)	12 (7.7)	2.05 (NS)
4	4 (4.9)	5 (3.2)	} 1.89 (NS)
5	4 (4.9)	3 (1.9)	

NS = Not significant.

Results

Of all 7725 men who were screened in the series, 127 had died by the end of 1980. For each of these we selected two living controls matched for age and date of screening and then from each group excluded those who had not been given the alcohol questionnaire. Of the remaining subjects, 82 who had died and 155 of the living controls had answered the questionnaire on alcohol consumption and form the basis of the following analysis.

Table II shows the distribution of men in the study and control groups among the seven categories of reported alcohol consumption. Overall, premature mortality was overrepresented in the total group of abstainers (seven deaths; 8.5%) as compared with among the total group of alcohol users. Table II also shows the observed to expected ratios as determined from the study and control groups. The highest ratio (2.20) was found among subjects who had reported abstinence in the questionnaire, and the lowest ratio (0.72) was found in those who had answered affirmatively to none of the questions on alcohol consumption. (significance of trend in the non-abstainers $p=0.006$). The observed to expected ratio increased with the category of stated alcohol consumption but did not reach the ratio found among the non-users.

Of the seven deaths among men who had reported abstinence in the questionnaire, four were caused by chronic illness (lung embolism, hepatitis, gastric cancer, gastric cancer), which in two cases (lung embolism and hepatitis) may have been related to a past history of alcoholism. The other three deaths occurred in men with malignant melanoma, epilepsy, and rheumatoid arthritis. The diagnosis was known at the time of the questionnaire in four of the cases (one of chronic alcoholism, one operated gastric cancer, one rheumatoid arthritis, treated with cytostatics, and one chronic hepatitis also treated with cytostatics).

Table III gives the mean screening γ -glutamyltransferase activities in the study group in relation to the various categories of stated alcohol consumption and proportions of deaths in these categories thought to be related to alcohol. With the exclusion of deaths among abstainers that may have been related to a past history of alcoholism, both the γ -glutamyltransferase activity and the proportion of alcohol-related deaths increased with ascending category of stated alcohol consumption.

TABLE III—Categories of stated alcohol consumption and γ -glutamyltransferase activities at time of screening and proportions of alcohol-related deaths among the 82 men who died

Category of alcohol consumption	Mean ($\pm$ SD) γ -glutamyltransferase activity (μ kat/l)	Proportion alcohol-related/total deaths	
		No	%
Abstinence	0.59 $\pm$ 0.56	1(2)/7	14.3 (28.6)
0	0.60 $\pm$ 0.43	1/27	3.7
1	0.60 $\pm$ 0.48	1/14	7.1
2	0.72 $\pm$ 0.63	3/13	23.1
3	0.68 $\pm$ 0.60	3/13	23.1
4	} 0.87 $\pm$ 0.66	3/4	75.0
5		4/4	100.0

Discussion

Despite the small size of this series, the subjects in the study and control groups were uniform in age and sex, had been recruited consecutively, and the results were highly significant. These suggested that conclusions on cardioprotective and other beneficial effects of low alcohol consumption may stem from increased ill health among non-users of alcohol. Including such non-users in studies of mortality may therefore create an impression that low levels of alcohol consumption are associated with a more favourable health state than no consumption at all. On the contrary, however, when we excluded this second category there seemed to be a continuous relation over the whole range of self-reported alcohol consumption, premature mortality being least in the lowest alcohol intake category and increasing with category. Most dramatic was the increase in alcohol-related deaths (table III). The validity of our questionnaire method has been evaluated and confirmed in our and other population studies.⁷ γ -Glutamyltransferase activity, which predominantly reflects biological effects of alcohol rather than the exact amounts consumed,⁸ also increased with intake category and tended to be low in the abstinent group.⁷

We think that the increased mortality in our abstinent group was related not to their non-use of alcohol but to the severe diseases in individual cases that made them give up alcohol in the first place. Of the seven abstainers in our study who died prematurely, four had organic diseases that might motivate abstinence from alcohol rather than be caused by alcohol. Such confounding factors will need realistic assessment in future investigations.

This work was supported by grants from the Swedish Council for Planning and Co-ordination of Research (BP) and the Swedish Delegation for Social Research, Ministry of Health and Social Affairs (HK).

References

- ¹ Klatsky AL, Friedman GD, Siegelau AB. Alcohol consumption before myocardial infarction. Results from the Kaiser-Permanente epidemiologic study of myocardial infarction. *Ann Intern Med* 1974;**81**:294-301.
- ² Hennekens CH, Rosner B, Cole DS. Daily alcohol consumption and fatal coronary heart disease. *Am J Epidemiol* 1978;**107**:196-200.
- ³ Hennekens CH, Willet W, Rosner B, Cole DS, Mayrent SL. Effects of beer, wine, and liquor in coronary deaths. *JAMA* 1979;**242**:1973-4.
- ⁴ LaPorte RE, Cresanta JL, Kuler LH. The relationship of alcohol consumption to atherosclerotic heart disease. *Prev Med* 1980;**9**:22-40.
- ⁵ Klatsky AL, Friedman GD, Siegelau AB. Alcohol and mortality. A ten-year Kaiser-Permanente experience. *Ann Intern Med* 1981;**95**:139-45.
- ⁶ Marmot MG, Rose G, Shipley MJ, Thomas BJ. Alcohol and mortality: a U-shaped curve. *Lancet* 1981;ii:580-3.
- ⁷ Kristenson H, Trell E. Indications of alcohol consumption. Comparison between a questionnaire (Mm-MAST), interviews and serum γ -glutamyltransferase (GGT) in a health survey of middle-aged males. *Br J Addict* (in press).
- ⁸ Kristensson H, Trell E, Hood B. Serum gamma-glutamyltransferase in screening and continuous control of heavy drinking in middle-aged men. *Am J Epidemiol* 1981;**114**:862-72.
- ⁹ Trell E, Dahlberg N, Larsson C, *et al*. Interactive computer system for monitoring multiphasic health screening. *Comput Programs Biomed* 1980;**12**:262-70.
- ¹⁰ Petersson B, Kristensson H, Sternby NH, *et al*. Alcohol consumption and premature death in middle-aged men. *Br Med J* 1980;**280**:1403-6.
- ¹¹ Anonymous. WHO and a new perspective on alcoholism. *Lancet* 1977;i:1087-8.

(Accepted 9 September 1982)

Premature Mortality in Middle-aged Men: Serum Cholesterol as Risk Factor*

Bo Peterson and Erik Trell

Section of Preventive Medicine, Department of Internal Medicine, University of Lund,
Malmö General Hospital, S-21401 Malmö, Sweden

Summary. Serum cholesterol as risk factor for premature mortality; 0–6, mean 3 years after a screening investigation in 10,000 middle-aged men (46–48 years at screening) was studied with respect to category of death. Serum cholesterol was reciprocally correlated to cancer deaths and to alcohol-related deaths, and strongly positively correlated to deaths in coronary heart disease. The men who died of cancer did not have lower body weight, nor was there any association with serum triglycerides. The inverse correlation to serum cholesterol did not differ between the cancer deaths occurring early, and those occurring later after screening. Part of the cholesterol/cancer death relationship may be explained by the presence of an otherwise occult malignancy at screening, but it cannot be excluded that the development of some cancers may be associated with a state of low serum cholesterol.

Key words: Cancer – Cholesterol – Risk factors

Introduction

Serum cholesterol is an established risk factor for coronary heart disease. It was therefore intriguing when it was demonstrated in one prospective study [1] that the relation between serum cholesterol and total mortality was in fact negative. The cholesterol/total mortality relationship was, in this study, found to consist of two contrary trends, a positive one for deaths in coronary heart disease, and a negative one for deaths in cancer. The negative correlation between serum cholesterol and death in cancer was interpreted as an effect of undetected disease at the time of screening [2] but the findings

in other studies that the association remain even after many years contradict this view.

We have earlier reported on the association of low cholesterol and death in cancer in the premature mortality in our population of middle-aged men in the Malmö Preventive Program (MAPP) [3]. We could also identify a third, not previously described, trend in this analysis of mortality – an inverse relation of serum cholesterol and alcohol-related deaths. It is thus obvious that different causes of death have different risk factor patterns that render an analysis of trends for total mortality of little value.

The purpose of the present report is to further examine and discuss the serum cholesterol/mortality relationship in our population which is characterized by its age- and sex homogeneity, its unselected cohort composition and good follow-up conditions.

Methods

Population

Details of the Malmö Preventive Program (MAPP) have been presented elsewhere [4, 5]. The Program started in 1974 at the Section of Preventive Medicine, Department of General Internal Medicine, Malmö General Hospital. Consecutive birth year cohorts of men living in Malmö were invited to the screening, which started with the cohort of men born 1926. These men were thus 48 years old at screening. The screening is a continuously ongoing process, but for the present study the birth year cohorts 1926–1932 were included. These cohorts comprised 10,353 men who were invited to the screening; in which 7,725 of the men participated, i.e., a participation rate of 74.6%. The men were 46–48 years old at screening. The screening is followed by an intervention program, as described elsewhere [6].

Screening Investigation

For the purpose of the present report the following screening procedures are considered Serum cholesterol and serum trigly-

* This study was supported by the Swedish Council for planning and coordination of Research and by the Kristianstads County Council

Table 1. Cancer sites

Site of cancer	No
Stomach	10
Lung	7
Pancreas	6
Haematological	6
Colon-rectum	4
Brain	3
Liver	2
Other	6
Total	44

cerides were analysed according to routine methods at the Department of Clinical Biochemistry. Serum gamma glutamyl transferase (GT) was analysed according to the recommendations of the Scandinavian Enzyme Committee [7]. A relative weight index, actual/deal weight (A/I-weight), was calculated according to standardized weight tables [4-6]. Smoking habits were obtained from a questionnaire.

Mortality Analysis

Deaths among the participants after screening were recovered from a file at the Department of Pathology, which covers all deaths in Malmö residents. The mortality for the years 1975-1980 was studied. The follow-up time was thus 0-6 years. During this period 127 participants died. The death rate was thus for the total cohort of participants 1.6%. This group was thoroughly analysed [4]. The autopsy rate was 86%. Three main groups of deaths were identified: 1) Deaths in cancer (44 men); the types of cancer are given in Table 1. One cancer death occurred 11 months after the screening, all others ≥ 1 year. 2) Deaths in coronary heart disease (CHD). 28 deaths were assigned to this group which consists of 15 cases of autopsy verified acute myocardial infarction, and 13 cases of death in other manifestation of coronary heart disease. 3) Alcohol-related deaths (ARD) were found in 28 men. This group is specified elsewhere [4]. All these men were problem drinkers, and their way of death was considered to be directly alcohol-related, either as consequence of a medical complication to alcohol consumption or directly caused by alcohol, or by way of the circumstances around the death pointing to alcohol as the dominant factor.

Statistical Methods

The screening distributions of serum cholesterol, triglyceride and gamma-glutamyltransferase (GT) in the total population of participants were divided into quintiles, and the screening values for the deaths allocated to the respective quintiles. These distributions were then compared in diagrams. A control group with two living controls for each dead participant, matched for age and screening date, was formed, and the controls allocated to the quintiles in the same way. Calculations of significance were then performed comparing the observed quintile distribution of the dead men with an expected distribution of a group of the same size according to the quintile distribution of the control group. For this calculation the standard test for trend in contingency tables [8] was used. For comparisons of means a *t*-test was used.

Results

The relation between serum cholesterol and mortality in this study is shown in Fig. 1. The relation

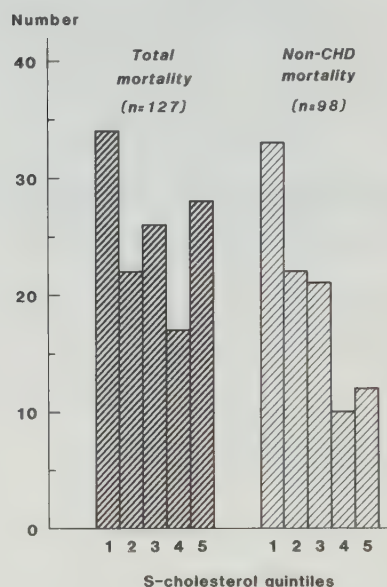


Fig. 1. Relation between serum cholesterol and total and non-coronary heart disease mortality. Serum cholesterol is distributed according to the quintiles in the original screening population of males in the same birth-year cohorts (The quintile limits were: ≤ 4.96 , $4.97-5.52$, $5.53-6.10$, $6.11-6.64$ and ≥ 6.65 mmol/l).

to total mortality is slightly negative with a tendency to U-form (Fig. 1a). If, however, deaths due to coronary heart disease are subtracted, the correlation between cholesterol and non-coronary mortality is significantly negative ($p < 0.001$). For the three main subgroups of deaths (Fig. 2) it is evident that deaths in coronary heart disease (Fig. 2c) showed the expected strong positive relation to cholesterol ($p < 0.001$), but the negative relation was present both in deaths due to cancer (Fig. 2a, $p < 0.05$) and in alcohol-related deaths (Fig. 2b, $p < 0.001$).

The cancer group was divided according to whether the time between screening and death was less than or more than 2.5 years (Fig. 3). The negative relationship between cholesterol and death in cancer was even stronger in the second ($p < 0.05$) than in the first group ($p < 0.1$). The relation between serum triglycerides and total mortality and mortality in the subgroups are given in Fig. 4 and Table 2. In contrast with cholesterol, triglycerides was a weak positive risk factor in relation to total mortality (not significant). In the subgroups, the positive correlation to CHD deaths was as prominent as for cholesterol ($p < 0.001$). Among cancer

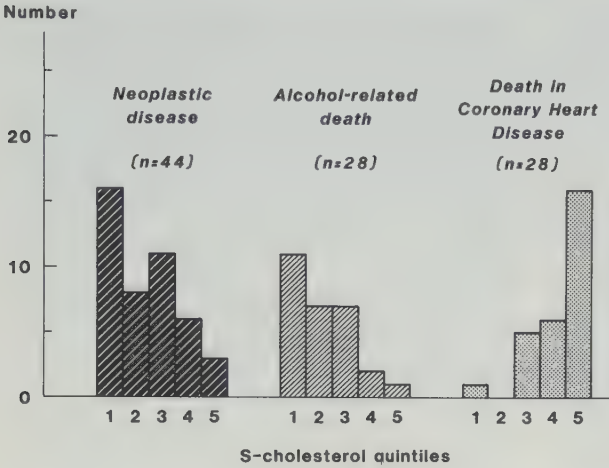


Fig. 2. Same relations between screening serum cholesterol and deaths in neoplastic disease, alcohol-related conditions and coronary heart disease

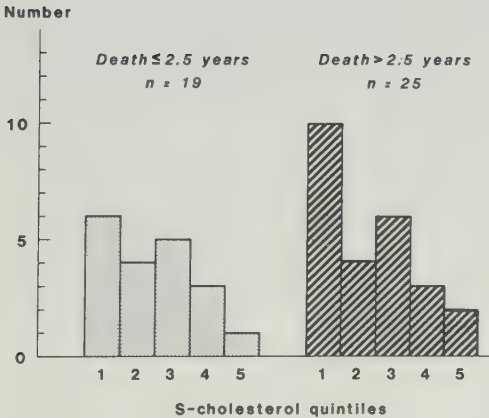


Fig. 3. Relation between the screening serum cholesterol and deaths in neoplastic disease occurring 11 months-2.5 years and 2.6-6 years after the screening, respectively

Table 2. Relation between serum triglycerides at screening (in quintiles of the normal distribution) and the main categories of death

Category of death	Quintile number				
	1	2	3	4	5
Neoplastic (n = 44)	11	7	5	8	13
Alcohol-related (n = 28)	7	5	5	5	6
Coronary heart disease (n = 28)	1	2	5	7	13

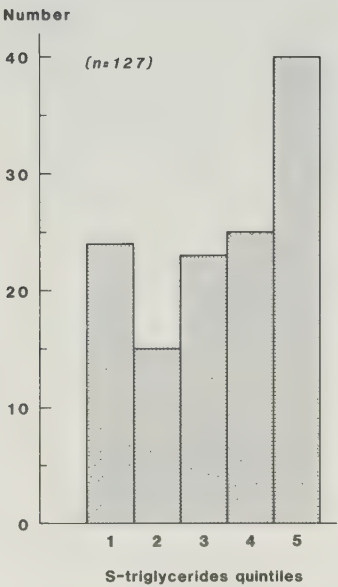


Fig. 4. Relation between screening triglycerides and total mortality

deaths there was a U-formed relationship, while for alcohol-related deaths there was no relation at all.

The mean relative weight was the same in the cancer group as in the controls (Table 3). There were no differences in the rate of smokers in the different cholesterol quintiles (not given).

Table 3. Screening body weight (relative body weight index) in neoplastic and alcohol-related deaths in comparison with matched living controls from the screening population

	Category of death		Controls (n = 254)
	Neoplastic (n = 44)	Alcohol-related (n = 28)	
A/I-weight	1.12 ± 0.15 ^a	1.10 ± 0.30 ^a	1.09 ± 0.15 ^a

^a S.D.

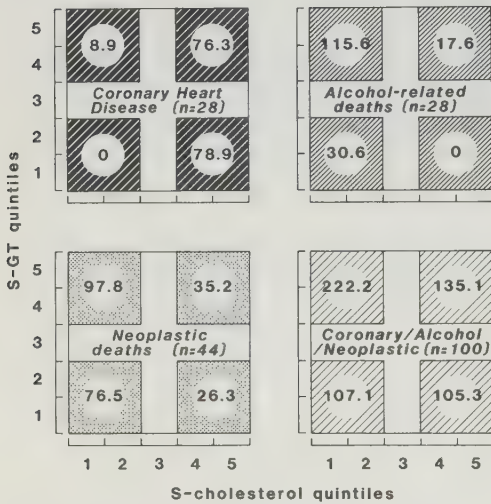


Fig. 5. Relations between screening serum cholesterol and gamma-glutamyltransferase (GT) and the main categories of death. The normal quintile limits of GT were: ≤ 0.36 , $0.37-0.45$, $0.46-0.60$, $0.61-0.94$ and ≥ 0.95 $\mu\text{kat/l}$, respectively. The numbers in the corners are observed number of deaths per 10,000 man-years at risk

Figure 5 is a graphic presentation of the relation between screening cholesterol and GT in the three main subgroups of deaths. For deaths in coronary heart disease high cholesterol was important irrespective of GT (Fig. 5a). A pattern of high GT and low cholesterol was typical for alcohol-related deaths (Fig. 5b), and the same pattern was also found for deaths in cancer (Fig. 5c). When the three subgroups are combined (Fig. 5d) it is seen that the most unfavourable "corner" was the one with high GT and low cholesterol, while the constellation of low GT and, relatively speaking, high cholesterol conferred the lowest death rate.

Discussion

The frequent finding in epidemiological studies of a negative correlation between serum cholesterol

and incidence of cancer disease has evoked much interest recently [1, 2]. We have earlier reported our preliminary observations on this finding in our population [3].

That serum cholesterol is a risk factor for coronary heart disease is well established. A review of this relationship has recently been given by Stamler [9]. However, different trends were observed when other endpoints were considered. In a study from Japan it was found that, in both men and women, subjects with low serum total cholesterol levels were more prone to cerebral haemorrhage [10]. Beaglehole et al. [1] showed in a population of Maoris in New Zealand that there was an inverse relation between serum cholesterol concentration and overall mortality both in men and in women. This inverse relation was also found for cancer and "other" causes of death. The follow-up time was 11 years. It was also reported in a study from Evans County, Georgia, that incident cancer cases (i.e. occurring more than 12 months after the measurement of serum cholesterol) had lower mean cholesterol levels than the non-cancer population [11]. This applied for both sexes, but the relationship tended to be stronger for males. It applied for all sites.

These findings were discussed by Rose and Shipley [2] against an analysis of the relation between serum cholesterol and mortality in the Whitehall study. They concluded that the inverse relation of non-CHD mortality and cholesterol level turned out to be an artefact dependent on the duration of follow-up. The association was present when the deaths occurred up to two years after the examination, but was absent after two years follow-up. The authors cited two other studies as confirmation of their conclusions, one from an insurance population in Oslo [12] based on a 10 year follow-up, and the Framingham study with 16 years follow-up [13], and they stated that none of these studies show any suggestion of true excess risk for men as a result of having lower plasma cholesterol. Rose and Shipley concluded that the association may be an unsuspected sickness phenomenon.

Similar conclusions were reached in a report from the Paris Prospective Study of Coronary Heart Disease [14]. One hundred and thirty-four cancer deaths were registered with a mean survival time of 6.6 years. The mean cholesterol value increased steadily with survival time. The initial cholesterol level did not differ significantly among cancer sites.

In our study we identify three groups with different distinctive trends in the association between serum cholesterol and death; one positive to deaths

in coronary heart disease, and two negative to neoplastic deaths and alcohol-related deaths. In contrast to the findings by Rose and Shipley [2] this association in our study is as evident in cancer deaths more than two and a half years after screening as in earlier deaths. The follow-up time in this study is 0 (eleven months)–6 years, and thus it is quite probable that the inverse relationship between serum cholesterol and cancer death will attenuate with longer follow-up time. If this phenomenon is a manifestation of subclinical disease, it is interesting that it is present so early in the course. It is not in our study associated with lower serum triglycerides or lower relative body weight.

It seems obvious that "total mortality" is a complex concept, consisting of different subgroups with different risk factor patterns. The characteristics of the population studied is thus important to bear in mind. Most of the cited studies are undertaken in "selected" populations, such as employees and insurance populations, include both sexes and broad age ranges. The male population in this study was recruited from total cohorts of men living in the town of Malmö, and all males were 46–48 years old when examined. It was thus an unselected population except for the nonparticipants.

The inverse relationship between neoplastic deaths and serum cholesterol in our study could not be attributed to differences in smoking habits, and did not differ according to cancer site. The numbers of cases in the different sites are small, however. Only males were included, and there may be a sex difference as in some of the cited reports. In a study of prognostic factors in breast cancer in women [15] it was found that women with low serum cholesterol and low body weight had better cumulative five-year disease-free survival than women with high body weight and high serum cholesterol.

In a previous study from Malmö of 41 deaths in 50–60 year old men [16], Lannerstad observed a negative association of serum cholesterol and death, and a bimodal association of serum triglycerides and death, although the numbers were too small for statistical significances to be attained. In the Stockholm Prospective Study, a study of the clientele from a health survey centre, it was also reported that – in men – there was a strong negative relation between cholesterol and death in neoplasia [17]. This association seemed to be due to gastro-intestinal cancer and did not disappear when deaths occurring the first two years were excluded.

Part of the explanation for the correlation of low cholesterol and cancer is undoubtedly ex-

istence of subclinical disease. In most studies the associations do attenuate with longer follow-up. Chronic disease is associated with low cholesterol values. In a study of pulmonary tuberculosis the reduction in serum cholesterol was related to the extent of the lesions [18]. In a consecutive sample of patients admitted to a general ward, the patients with hypocholesterolemia had an increased mortality [19]. Low serum cholesterol may thus be among the first signs of further deterioration of disease. Similar conclusions are drawn by Gilbert et al. [20] in cases of myeloproliferative disease, and they state that "total cholesterol levels may provide an assessment of disease activity that is of greater biologic significance than measurement of circulating cell populations and organ size". As these and other [21] authors point out, another hypothesis for this relation could be that low serum cholesterol is a bioregulator for the development and inhibition of leukemia. Further studies are necessary to elucidate this.

Alcoholism is another chronic disease and the finding in our population of an association between low cholesterol/alcohol-related death may be interpreted against this background. Nevertheless, no other study has hitherto identified this category of deaths as one of the main groups behind the relation of low cholesterol and non-coronary, non-cancer death. This is in our study not associated with lower mean relative weight in the alcohol-dead at screening, nor with higher or lower serum triglycerides. In our study group, alcohol-related death is a major cause of death [4], second only to cancer and equally large as coronary heart disease. The population in which our study was undertaken, i.e. about 50 year old men, is the sex- and age-group where the death-rate due to alcohol consumption is at its peak [22], and in epidemiological investigations in such populations it is extremely important to attempt to evaluate the extent of high alcohol consumers.

The influence of ethanol on serum cholesterol concentration in man was investigated by Grande and Amatuzio [23] who in a study on volunteers found a small but statistically significant increase in cholesterol concentration with ethanol ingestion. They also found that the degree of elevation of cholesterol was dependent on pre-existing hyperlipidemia. In a carefully controlled experimental study on male students, ethanol administration in the form of beer in an amount corresponding to 60 g absolute ethanol per day during six weeks did not increase the serum total cholesterol level. In The Cooperative Lipoprotein Phenotyping Study [24] there was in none of the populations any correlation between (self reported) alcohol consump-

tion levels and total serum cholesterol, although there were changes in the different lipoprotein classes of cholesterol. In conclusion, it seems that there is a small cholesterol elevating effect of moderate amounts of alcohol in healthy individuals, but individuals with more advanced alcohol-related illness may tend to have low serum cholesterol, probably dependent on dietary factors and influence of the chronic disease state present in chronic alcoholism, and perhaps also on factors such as infections or gastro-intestinal disorders.

When both cholesterol and gamma glutamyl-transferase (GT) are considered, different patterns for the three subgroups of death emerge. Coronary deaths are characterized by high cholesterol, but there doesn't seem to be any association with GT. For alcohol-related deaths, the main risk is found in the "corner" with low cholesterol and high GT. Deaths in cancer occurred with low cholesterol and a weak positive correlation with GT was also present. The most "dangerous" combination, when these three subgroups of death are taken together, was a constellation of, relatively speaking, low cholesterol and high GT.

In a recent issue of the American Journal of Epidemiology three additional reports described the association of low cholesterol and cancer mortality [25–27]. The relation was strong in all the three studies. In the Honolulu Heart Program [25] serum cholesterol was inversely correlated to total cancer mortality during a follow-up time of nine years in men. When the mortality for the first two years was excluded the association remained only for colon cancer and lung cancer. In the Yugoslavia Cardiovascular Disease Study [26], middle-aged men were followed for seven years after an examination. Serum cholesterol was negatively related to total mortality, and this was due to deaths in cancer and deaths in respiratory disease. The correlation was also present in the mortality analysis in the Puerto Rico Heart Program [27], also in males, monitored for eight years. In contrast to this is a report from the populations of industrial workers in Chicago [28] where there was no association between cholesterol and deaths in cancer or in other causes of death other than cardiovascular.

The latest and most comprehensive survey of this field is the large International Collaborative Group report [29], representing the findings in samples of men ranging in number between 401–18,309 (two studies > 10,000), age 40–69 years and follow-up time (5–) 9–10 years. A strong inverse relation between cholesterol and cancer mortality was present in the 0–1 year's follow-up peri-

od, persisted on a lower level during the years 1–5, but was not significant during years 6–10. Our results largely correspond to the middle of these groups, since there was only one case in our health screening material who died of cancer <1 year (11 months) from the screening [30]. However, we believe that our data are of complementary value since the health screening sample is the largest reported of its more narrowly defined age- and sex-range, and the findings were statistically highly significant and persisted throughout the 6-year period studied. The inverse correlation was present with equal strength even in the time >2.5 years after the screening. Careful re-evaluation of all the screening protocols has revealed other signs of malignant disease at the time of investigation only in a fraction of the cases dying <2.5 years after this [30].

It seems unlikely that undetected neoplastic conditions of a degree sufficient to alter serum cholesterol level were present in a large proportion of the even later cases. Thus we believe that our observations may allow the hypothesis that there might be a state, possibly transiently during a period a few years before the onset of cancer, during which there might be a state of increased metabolic and cellular activity which is reflected in or otherwise connected with a lowered serum cholesterol value, but represents a stage prior to established malignancy. Furthermore we think that the findings, in the same uniform study group, of statistically highly significant differential trends of serum cholesterol in relation to the other major categories of male premature mortality, i.e. cardiovascular and alcohol-related deaths, are of considerable interest and also warrant further elucidation, e.g. on pathophysiological mechanisms, lipoprotein classification and patterns, and possible preventive implications.

References

1. Beaglehole R, Foulkes MA, Prior IAM et al. (1980) Cholesterol and mortality in New Zealand Maoris. *Br Med J* 1:285
2. Rose G, Shipley MJ (1980) Plasma lipids and mortality: a source of error. *Lancet* 1:253
3. Petersson B, Trell E, Sternby NH (1981) Low cholesterol level as risk factor for noncoronary death in middle-aged men. *JAMA* 245:2056
4. Petersson B, Krantz P, Kristenson H, Trell E, Sternby N-H (1982) Alcohol-related death: A major contributor to mortality in urban middle-aged men. *Lancet* II:1088
5. Petersson B, Trell E, Krantz P, Sternby N-H, Hood B (1983) Major determinants of premature mortality in middle-aged urban males. Alcohol-related deaths, non-participation, and possible intervention effects in preventive population program directed against alcohol and its complications. (Submitted)

6. Kristensson H, Trell E, Hood B (1981) Serum gamma - glutamyltransferase in screening and continuous control if heavy drinking in middle-aged men. *Am J Epidemiol* 114:868
7. The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology (1976) Recommended method for the determination of gamma glutamyltransferase in blood. *Scand J Clin Lab Invest* 78:119
8. Maxwell AE (1961) Analyzing qualitative data. Methuen, London
9. Stamler J (1980) The established relationship among diet, serum cholesterol and coronary heart disease. *Acta Med Scand* 207:433
10. Ueshima H, Iida M, Shimamoto T et al. (1980) Multivariate analysis of risk factors for stroke. *Prev Med* 9:722
11. Kark JD, Smith AH, Hames CG (1980) The relationship of serum cholesterol to the incidence of cancer in Evans County, Georgia. *J Chron Dis* 33:311
12. Westlund K, Nicolaysen R (1972) Ten-year mortality and morbidity related to serum cholesterol. *Scand J Lab Invest* 30: [Suppl] 127
13. Williams RR, Sorlie PD, Feinlieb M et al. (1981) Cancer incidence by levels of cholesterol. *JAMA* 245:247
14. Cambien F, Ducimetriere P, Richard J (1980) Total serum cholesterol and cancer mortality in a middle-aged male population. *Am J Epidemiol* 112:388
15. Tartter PI, Papatestas AE, Ioannovich J (1981) Cholesterol and obesity as prognostic factors in breast cancer. *Cancer* 47:2222
16. Lannerstad O, Isacson SO, Lindell SE (1979) Risk factors for premature death in men 56-60 years old. *Scand J Soc Med* 7:41
17. Böttiger LE, Carlsson LA (1980) Mortality and entry characteristics in the Stockholm Prospective Study. *Skandia International Symposia: Medical aspects on mortality statistics*, Stockholm, p 89
18. Singh V, Goyal RK, Mathur MN (1977) Serum cholesterol in patients with pulmonary tuberculosis. *J Indian M* 69:220
19. Oster P, Muchowski H, Heuck CC (1981) The prognostic significance of hypocholesterolemia in hospitalized patients. *Klin Wochenschr* 59:857
20. Gilbert HS, Ginsberg H, Fagerstrom R et al. (1981) Characterization of hypocholesterolemia in myeloproliferative disease. Relation to disease manifestations and activity. *Am J Med* 71:595
21. Inbar M, Shinitzky M (1974) Cholesterol as bioregulator in the development and inhibition of leukemia. *Proc Natl Acad Sci USA* 71:4229
22. Poikolainen K (1977) Alcohol poisoning mortality in four nordic countries. The Finnish foundation for alcohol studies
23. Grande F, Amatuzio DS (1960) The influence of ethanol on serum cholesterol concentration. *Minnesota Med* 11:731
24. Castelli WP, Gordon T, Hjortland MC et al. (1980) Alcohol and blood lipids. The Cooperative Lipoprotein Phenotyping Study. *Lancet* II:153
25. Kagan A, McGee DL, Yano K et al. (1981) Serum cholesterol and mortality in a Japanese - American population. *Am J Epidemiol* 114:11
26. Kozarevic D, McGee D, Vojvodic N et al. (1981) Serum cholesterol and mortality. The Yugoslavia Cardiovascular Disease Study. *Am J Epidemiol* 114:21
27. Garcia-Palmieri MR, Sorlie PD, Costas R et al. (1981) An apparent inverse relationship between serum cholesterol and cancer mortality in Puerto Rico. *Am J Epidemiol* 114:29
28. Dyer AR, Stamler J, Oglesby P et al. (1981) Serum cholesterol and risk of death from cancer and other causes in three Chicago epidemiological studies. *J Chron Dis* 34:249
29. International collaborative group (1982) Circulating cholesterol level and risk of death from Cancer in men aged 40 to 69 years. Experience of an international collaborative group. *JAMA* 248:2853
30. Petersson B, Trell E (1983) Raised serum urate concentration as risk factor for premature mortality in middle-aged men: relation to death from cancer. *Br Med J* 287:7

Received August 30, 1982

Revised February 22, 1983

Accepted May 25, 1983

Assoc. Prof. Dr. E. Trell
Section of Preventive Medicine
University of Lund, Malmö General Hospital
S-21401 Malmö
Sweden

Raised serum urate concentration as risk factor for premature mortality in middle aged men: relation to death from cancer

BO PETERSSON, ERIK TRELL

Abstract

Low serum cholesterol concentrations are associated with deaths from cancer. This association was found in a prospective study of middle aged men in Malmö and consideration of possible explanations for the lowering of serum cholesterol prompted an analysis of serum urate in relation to deaths from cancer. A total of 127 of the 7725 participants in the Malmö study had died since screening. A weakly positive but significant correlation between raised serum urate concentration and total mortality was found. This correlation was wholly explained by neoplastic deaths ($p < 0.01$), while there were no associations with alcohol related deaths or with deaths from coronary heart disease. When the deaths from cancer were classified as "early" or "late"—that is, occurring less than or more than 2.5 years after the screening—the correlation between raised urate concentrations and cancer mortality was confined to the "early" deaths ($p < 0.001$). Further studies are needed to substantiate the relation between raised serum urate concentrations and fatal neoplasia. Nevertheless, these findings weigh against recent suggestions that uric acid has an antioxidant protective effect against cancer.

Section of Preventive Medicine, Department of Internal Medicine,
Malmö General Hospital, S-214 01 Malmö, Sweden

BO PETERSSON, MD, associate researcher

ERIK TRELL, associate professor of preventive medicine

Correspondence and requests for reprints to: Dr Bo Petersson.

Introduction

We have previously reported an association between low serum cholesterol concentration and deaths from cancer in the prospective study of middle aged men in Malmö.¹ This association has also been documented in other populations, and its most immediate explanation is that it reflects an effect of cancer undetected at the time of the screening.² This suggests that some cancers have a very long preclinical stage, because in some studies this correlation is present up to a decade before the death.³ One way in which serum cholesterol might be lowered is by uptake of low density lipoprotein cholesterol by the rapidly proliferating cancer cells. If this is the case and there is no increase in body weight or rather a weight loss there must be concomitant increase in cell breakdown. These considerations prompted us to analyse serum urate concentration in relation to deaths from cancer, as urate is a breakdown product of tissue nucleotides.

Methods

Details of the Malmö Preventive Programme have been given elsewhere.^{1,4} We studied mortality in the men born from 1926 to 1932 who had been screened by us from 1975 to 1980. A total of 7725 (75% of total cohort) attended the screening and we used these as our study group. The follow up time was thus 0-6 years and during this period 127 participants died, corresponding to a death rate of 1.6%. A total of 109 necropsies were conducted. The necropsy rate was 86%. Three main groups of deaths were identified: deaths from neoplasm (International Classification of Diseases 140-239), deaths from coronary heart disease (ICD 410-414), and alcohol related deaths. For classification as alcohol related the following criteria were applied: a history of high alcohol consumption and death either directly related to alcohol—for example, death from intoxication or from trauma while intoxicated—or from a cause complicated by alcohol—for example cirrhosis—or where alcohol was deemed to be the major factor behind the events leading to death.⁴

Serum urate concentration was determined enzymatically with a commercially available reagent (Boehringer Mannheim) and serum cholesterol concentration was also analysed by a routine enzymatic method at the department of clinical biochemistry at the Malmö General Hospital. For calculation of statistical significance a standard test for trend in contingency tables was used.⁵ Quintile distributions of serum urate and cholesterol concentrations for the total population of those in the same birth-year cohorts who had taken part in the screening were used as reference.

Results

Raised serum urate concentration was positively correlated to total mortality, and this correlation was statistically significant ($p < 0.05$, table I). When the deaths were divided into the three categories mentioned above, this positive correlation was found to be wholly dependent on the deaths from cancer ($p < 0.01$); there were no correlations with deaths from coronary heart disease or with alcohol related deaths. When the deaths from cancer were divided into those occurring less than 2.5 years after screening ("early" deaths) and those occurring more than 2.5 years after screening ("late" deaths) it was found that the association between high serum urate concentration and cancer was confined to the early deaths ($p < 0.001$, table II). Table III shows the clinical characteristics of those dying less than 2.5 years after screening. Altogether 13 of the 19 early cancers were present at or within one year of screening.

The mean (SD) relative weight—that is, actual over ideal weight—of the men who died of cancer was 1.12 (0.15), that of those who died of alcohol related conditions was 1.10 (0.30), and that of a matched control group of surviving men was 1.09 (0.15). There was no difference in the relative weight of those who died from cancer.

The early deaths from cancer showed an inverse correlation between serum cholesterol and serum urate, which is illustrated in the figure ($p < 0.1$).

Serum creatinine concentrations of those who died from cancer were not significantly different from those of men in the other mortality groups. Furthermore, there were no differences between the groups in medication with diuretics or other drugs (not shown).

TABLE I—*Relation of serum urate concentration (quintiles) to mortality in middle aged men taking part in the Malmö Preventive Programme*

Serum urate ($\mu\text{mol/l}$)	All deaths (n)	Main categories of causes of death		
		Neoplasm (n = 44)	Alcohol related (n = 28)	Coronary heart disease (n = 28)
≤ 257	22	6	6	5
258–292	20	5	5	6
293–323	21	7	4	7
324–358	28	8	6	7
≥ 359	36	18	7	3

TABLE II—*Distribution of serum urate concentrations in men who died of cancer by time of death*

Serum urate ($\mu\text{mol/l}$)	Early deaths*	Late deaths*
≤ 257	0	6
258–292	1	4
293–323	4	3
324–358	4	4
≥ 359	10	8
Total	19	25

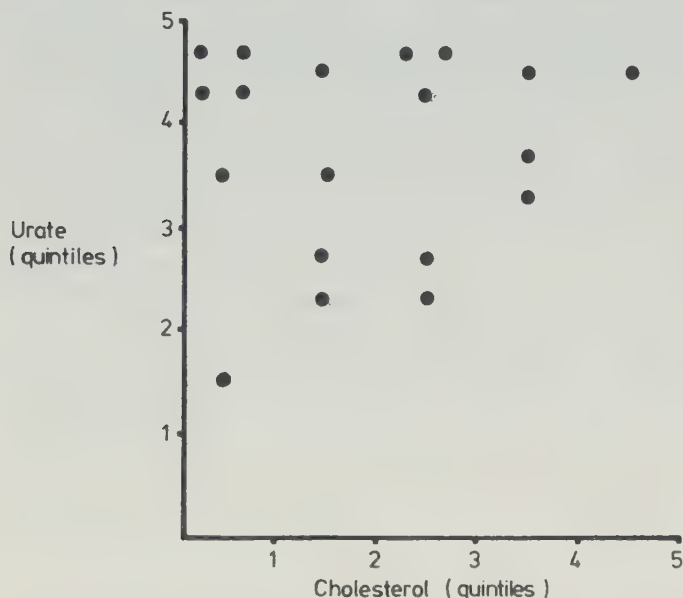
*Early = ≤ 2.5 years after screening; late = > 2.5 years after screening.

TABLE III—*Clinical characteristics of 19 men who died of cancer within 2-5 years after screening*

Case No	Type and site of cancer	Clinical data	Time from screening (months)	
			Diagnosis	Death
1	Brain tumour		4	16
2	Malignant histiocytosis		7	21
3	Cancer of the pancreas		8	13
4	Abdominal adenocarcinoma		19	22
5	Malignant melanoma		6	24
6	Cancer of the pancreas		20	29
7	Primary hepatic carcinoma		26	26
8	Cancer of the colon	Diagnosed at screening (high serum γ -glutamyltransferase)	17	30
9	Cancer of the pancreas		21	29
10	Gastric cancer	Underwent operation for gastric cancer three years earlier		24
11	Bronchial cancer	Diagnosed at screening (haemoptysis)		12
12	Gastric cancer		19	25
13	Cancer of the pancreas	Diagnosed at screening (hypercalcaemia)		15
14	Malignant lymphoma	Known at screening		21
15	Cancer of the colon	Diagnosed at screening (anaemia)		12
16	Gastric cancer		8	11
17	Bronchial cancer		9	20
18	Gastric cancer		15	20
19	Carcinoma of the bladder	Diagnosed at screening (haematuria)		14

Discussion

In this study of men aged about 50 years we found a weakly positive association between raised serum urate concentration and total mortality. This was wholly dependent on the association with deaths from cancer, which was statistically significant. We believe that this may be regarded as an indication



Distribution (in quintiles) of serum cholesterol and serum urate concentrations in the "early" deaths from cancer (n=19). Cholesterol reference quintiles: ≤ 4.96 , 4.97-5.52, 5.53-6.10, 6.11-6.64, and ≥ 6.65 mmol/l. Urate reference quintiles as in tables.

of tumour undetected at the time of the screening, because the correlation was further confined to those deaths that occurred less than 2.5 years after screening. To our knowledge this association has not been reported before in a prospective study, and asymptomatic hyperuricaemia is usually not considered to be an indication of cancer, with the exception of myeloproliferative disorders.^{6,7} Despite the short follow up time, our findings speak strongly against a recent hypothesis that serum uric acid is anticarcinogenic.⁸

We have previously reported that serum cholesterol in our study group was inversely correlated to the deaths from cancer,

both early and late.¹ One possible explanation for the constellation of low serum cholesterol and high serum urate values may be that a cancer lowers serum cholesterol concentration by way of uptake into the proliferating tumour cells.

The lack of association between raised serum uric acid concentration and the two other major mortality categories in this study—deaths from coronary heart disease and alcohol related deaths—is notable. Nevertheless, the published evidence for raised uric acid concentration as a risk factor for coronary heart disease is conflicting.⁹

Alcohol, on the other hand, is usually considered to raise the serum urate concentration. Alcoholics have an increased incidence of hyperuricemia,¹⁰ and hyperuricemia in clinical settings is regarded as an indicator of alcohol abuse.^{11 12} According to Lieber, alcohol raises the lactate concentration in serum thus hampering the renal excretion of uric acid.¹³ One study, however, reported an enhanced renal excretion of uric acid in liver cirrhosis¹⁴ and in some population studies no correlation is found between (self reported) alcohol consumption and serum urate concentration.^{15 16} Our findings indicate that there are no strong associations between raised serum urate concentration and advanced stages of alcohol related diseases.

Further studies are necessary to substantiate the relation between urate and fatal neoplasia in larger groups with different types of tumours. The clinical significance of the findings may be limited because of the need for large, age and sex matched reference materials. Nevertheless, monitoring longitudinal changes in serum urate and cholesterol concentrations in conjunction with other risk indicators such as cigarette smoking and hereditary factors may be of practical use for the early detection or prevention of cancer. Furthermore, the results may be of theoretical interest as they weigh against recent suggestions that serum uric acid has an antioxidant protective effect against cancer.⁸

This study was supported by the Swedish Council for Planning and Coordination of Research and by the Kristianstads County Council.

References

- ¹ Petersson B, Trell E, Sternby NH. Low cholesterol level as risk factor for non-coronary mortality in middle-aged men. *JAMA* 1981;**245**: 2056-7.
- ² Rose G, Shipley MJ. Plasma lipids and mortality: a source of error. *Lancet* 1980;ii:523-6.

- ³ Kark JD, Smith AH, Hames CG. The relationship of serum cholesterol to incidence of cancer in Evans County, Georgia. *J Chronic Dis* 1980; **33**:311-22.
- ⁴ Petersson B, Krantz P, Kristensson H, Trell E, Sternby NH. Alcohol-related death: a major contributor to mortality in urban middle-aged men. *Lancet* 1982;ii:1088-90.
- ⁵ Maxwell AE. *Analyzing qualitative data*. London: Methuen, 1961.
- ⁶ Seegmiller JE. Disorders in purine and pyrimidine metabolism. In: Bondy PK, Rosenberg LE, eds. *Metabolic control and disease*. Philadelphia: Saunders, 1980:780.
- ⁷ Fessel WJ, Siegelau AB, Johnson ES. Correlates and consequences of asymptomatic hyperuricemia. *Arch Intern Med* 1973; **132**:44-54.
- ⁸ Ames BN, Cathcart R, Schiewers E, et al. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proc Natl Acad Sci USA* 1981; **11**:6858-62.
- ⁹ Persky VW, Dyer A, Idris-Soven E, et al. Uric acid: a risk factor for coronary heart disease? *Circulation* 1979; **59**:969-77.
- ¹⁰ Olin JS, Devenyi P, Weldon KL. Uric acid in alcoholics. *Quarterly Journal of Studies on Alcohol* 1973; **34**:1202-7.
- ¹¹ Drum DE, Goldman PA, Jankowski CB. Elevation of serum uric acid as a clue to alcohol abuse. *Arch Intern Med* 1981; **141**:477-9.
- ¹² Ramsay LE. Hyperuricemia in hypertension: role of alcohol. *Br Med J* 1979;ii:643-4.
- ¹³ Lieber CS, Jones DP, Losowsky MS, et al. Interrelation of uric acid and ethanol metabolism in man. *J Clin Invest* 1962; **41**:1863-70.
- ¹⁴ Higuchi T, Nakamura T, Uchino H. Enhanced renal clearance of uric acid in hepatic cirrhosis. *Isr J Med Sci* 1981; **17**:1015-8.
- ¹⁵ Munan L, Kelley A, Petitclerc C. Population serum urate levels and their correlates. The Sherbrooke regional study. *Am J Epidemiol* 1976; **103**:369-82.
- ¹⁶ Bengtsson C, Tibblin E. Serum uric acid levels in women. *Acta Med Scand* 1974; **196**:93-102.

(Accepted 20 April 1983)

